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*A COMPARATIVE HISTOPATHOLOGICAL STUDY OF "INFANTILE CIRRHOSIS OF THE LIVER" OF INDIA WITH CIRRHOSIS OF THE LIVER IN INFANTS OF EDINBURGH

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Introduction

Infantile cirrhosis of the liver in India was described for the first time by Sen in 1887, and was examined microscopically by Gibbons in 1888. Many valuable contributions have been made to the medical literature with regard to the etiology, pathology, and pathogenesis of this disease in recent years. Tirumurthi, T.S. and Radhakrishna Rao, M.V., studied the pathological changes in the liver in 1934, and later Radhakrishna Rao (1935) who investigated the morbid condition of the liver in this disease came to the conclusion that it was one of "subacute toxic cirrhosis" showing biliary inflammation only occasionally. The tendency to affect children of the same mother suggested to Bhaskara Menon (1931) an antenatal cause acting slowly after birth, and the histological resemblance in some respect to congenital syphilitic cirrhosis led him to suspect a toxin carried by the umbilical vein—an umbilical vein cirrhosis.

There has been a tendency among Indian investigators to regard this disease as being peculiar to India, (Radhakrishna Rao, 1935), even though many American and European writers from time to time have drawn our attention to a type of juvenile cirrhosis occurring in successive children of the same mother.

Rossele (1933) who has reviewed the literature on pathology of cirrhosis thoroughly, finds evidence for a a hereditary tendency lacking. When it occurs in a family it frequently affects more than one child. Weber (1936) suggested an inborn familial tendency to the development of hepatic cirrhosis in infancy and childhood, and classified the familial incidence as due to either a congenital tissue or organ inferiority of the liver or as an example of hepatic cirrhosis accompanying and probably constituting a part of acknowledged disease of the congenital developmental case.

Moon (1929) reported two cases of cirrhosis in children whose livers showed histologically in sections stained for bacteria, cocci in pairs in one case, and in the other streptococci, while on culture a pure growth of streptococcus haemolyticus was obtained from the latter's liver. It is interesting to note in this case that several children in the family had already died of cirrhosis of the liver. Bingel (1907) was convinced that many cases of cirrhosis in children occur after epidemics of scarlet fever. Thompson (1908) believed in infectious jaundice in newly-born infants as a result of infection from the umbilicus.

According to Moon (1933) the United States of America Mortality Statistics for 1929 show 64 deaths from cirrhosis of the liver among children under fifteen of which 23 were under 2 years of age. Though the exact figures for the different types of cirrhosis in children were not available, he found that in the majority of cases under one year of age the cirrhosis was due to congenital obliteration of the bile ducts, and that those occurring after the first year were due to portal or Laennec's cirrhosis. Deaver (1933) Leversen (1908) and Ladd (1928) cited cases of cirrhosis in infants due to congenital obliteration of the bile duct.

Bridgeman and Robertson (1932) and Sutton, (1930) reported cases of atrophic or Laennec's cirrhosis in infancy with hereditary tendency.

Rolleston and McNee (1929) quoted (Ponynton and Wyllie) a report of 22 cases of congenital biliary cirrhosis at the Great Ormond Street Hospital for Sick Children during the period 1910 to 1925. Of these cases 15 were due to congenital obliteration of the bile ducts, and 7 were due to other causes. They believed that the obliteration of the bile duct was secondary to the cirrhosis which was of obscure origin. At the Royal Hospital for Sick Children, Edinburgh, during a period of 14 years, from January 1927 to December 1940 there were 9 cases of cirrhosis of doubtful origin in children under two years, 14 of congenital syphilitic cirrhosis, and 3 due to congenital obliteration of the bile ducts.

It can be deduced from the enormous literature available on the subject of cirrhosis of the liver in infants and children that it is not such an uncommon disease either in Europe or in America as one would suspect it to be.

As to the nature of this disease opinion seems to differ. In many of these cases there appears to be an inherent tendency in children of the same mother to be affected by the disease. Syphilis though the commonest and best understood etiological factor has been ruled out in these cases. Infectious diseases and infections of the liver have been the cause of cirrhosis in a number of cases. Some livers have been classified

*This work was carried out in the University of Edinburgh during the period 1939 to 1941, and formed part of a thesis on "The studies on infantile cirrhosis of the liver, and on the effect of cirrhogenic toxin on the progeny."

under the vague and obscure term "Hanot's cirrhosis." Many were due to congenital obliteration of the bile ducts, and a few to portal or Laennec's cirrhosis and to toxic cirrhosis.

A study of the histopathology of the cases from Edinburgh along with those of "Infantile Cirrhosis" of India is undertaken in order to determine if the latter disease is peculiar to India only and if it is not so to find out the possibility of a common etiological factor responsible for these cases.

TABLE OF DISORDERS OF THE LIVER FROM THE POSTMORTEM RECORD OF THE ROYAL HOSPITAL FOR SICK CHILDREN, EDINBURGH, FROM JANUARY 1927 TO DECEMBER 1940

Year	P.M.	Cirrhosis of unknown etiology	Cong. syph. cirrhosis	Cong. oblit. bile duct	Acute & sub-acute atrophy	Icterus gravis	Other disorders
1927 ..	157	1	1	..	1	1	..
1928 ..	146	1	2	1	1	..	..
1929 ..	181	..	..	..	..	1	..
1930 ..	166	..	1	..	..	..	..
1931 ..	149	1	3	..	..	1	..
1932 ..	157	..	..	..	..	1	..
1933 ..	154	2	2	..	..	..	..
1934 ..	127	..	..	..	..	..	1 central necrosis
1935 ..	159	1	1	..	..	..	1 cholecystitis
1936 ..	149	1	1	1	..	..	..
1937 ..	193	..	..	..	1	..	1 central necrosis
1938 ..	185	1	3	..	..	1	2 fatty livers
1939 ..	150	..	..	1	3	1	..
1940 ..	175	1	..	..	..	..	..
Total 14 yrs. ..	2240	9	14	3	6	6	6

MATERIAL AND METHODS OF STUDY

The material for study consisted of sections from sixteen cases: six from India and ten from the Royal Hospital for Sick Children, Edinburgh. Though the mortality rate for 'Infantile biliary cirrhosis' is great in Calcutta (700 deaths or more per year) and Madras, there is scarcity of post mortem material. Of the six cases available, two were obtained from Pathology Department of the Vizagapatam Medical College through the kind permission of Prof. Bhaskara Menon, and the other four were supplied by Prof. Ramachandra Rao of the Madras Medical College. These sections were fixed in formalin, and preserved in glycerine and water.

Of the ten cases from the Royal Hospital for Sick Children, Edinburgh, one was an authentic case of congenital obliteration of bile duct, and the other nine cases of cirrhosis of obscure etiology in children under two years of age. Paraffin blocks for eight of these cases and section of the liver and other organs stained with haematoxylin and eosin in the case of the remaining two were placed at my disposal by Dr. MacGregor.

STAINING METHODS USED

(1) For routine staining. Meyer's acid alum haematoxylin and eosin.

(2) For connective tissue. Heidenhain's Azan method.

(3) Verheoff's elastic tissue stain.

(4) Sudan III. counterstained with haematoxylin for fat.

(5) Dobell's modification of Levaditi for spirochaetes.

(6) Koppeleoff and Beirmann's modification of Gram's method for bacteria.

(7) Foot and Menard's technique for reticulum.

Six of the sections from India which were preserved in glycerine and water were washed in water for 48 hours and postfixed in Helly's fluid before embedding in paraffin.

MORBID ANATOMY AND CYTOLOGY OF THE LIVER

Case 1—V.A. Female infant. Aged 2 years.

POST-MORTEM: *Morbid anatomy*—Smooth capsular surface. Edges sharp. Uniform bile staining of the parenchyma on section. Sclerotic thickening of the larger portal spaces.

Histology—The parenchyma is permeated with bands of wavy fibrous tissue isolating the hepatic cords into groups of varying size. In places the collagen fibres have insinuated themselves in between individual liver cells giving the whole field the appearance of intersitial cirrhosis. The parenchymal cords are widely separated by the gaping sinusoids and many of them show degenerative changes and vacuolation. The nuclei are faintly stained, the cytoplasm granular and eosinophilic. The potential lumen in the hepatic cords is filled in places by a plug of inspissated bile. In sections from different parts of the liver the microscopical changes are slightly different; the islands of regenerated liver cells being larger and degeneration less pronounced. Here and there among the degenerated liver cells oval or rounded islands of parenchymal cells are found to be in various stages of necrosis. The healthy cells around such islands are compressed and stretched over them, a condition suggesting an oedema of the involved cells prior to their disintegration. There is moderate infiltration with polymorphs and lymphocytes in the necrotic debris.

Bile Ducts: Proliferation of biliary canaliculi varies in different sections. Numerous long and tortuous or short and tubular bile ducts are embedded in thick wide bands of cellular fibrous tissue. In other parts, the fibrous tissue bands are devoid of any proliferated bile ducts. The ducts in the portal tract are unaffected, their lining epithelium being healthy and there is absence of any infiltration with inflammatory cells. A few of the proliferated bile ducts contain insipissated bile, showing a direct continuity with healthy liver cells.

Hepatic Vein: Branches of the hepatic vein are scarcely to be seen in the section, but wherever they are found they are seen to be surrounded by dense fibrous tissue and their wells are thick and sclerosed. A few of the larger branches show endophlebitis and infiltration of the intima with inflammatory cells. Hepatic terminals are scarce, their walls being involved in similar sclerosis with obliteration of the lumen. The parenchymal cells around such central veins have completely disappeared, being replaced by cellular fibrous tissue.

The Portal Tracts: There is no marked increase of fibrous tissue in the Glisson's capsule. There is no periductal sclerosis. The hepatic artery and portal vein show no noticeable change. There is slight fibrosis of the periphery of the lobules in the region adjacent to the portal tract which tends to magnify the apparent width of the tract.

As the histopathology of infantile cirrhosis of India has been frequently described by various writers, it is considered

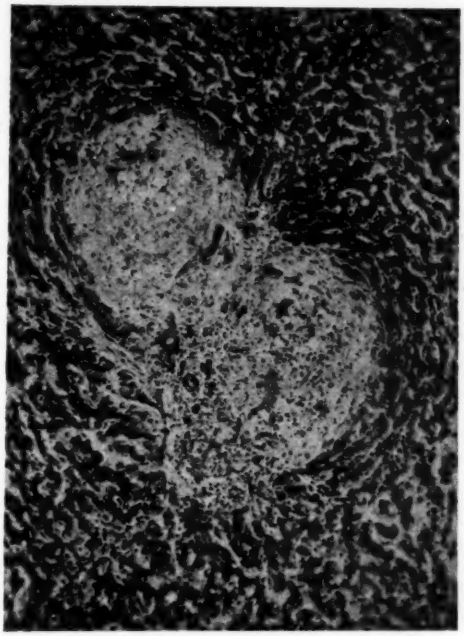

FIG. 1—Liver of Case I. Massive necrosis of liver cells. The healthy cells are compressed and stretched out over the islands of necrosis. There is moderate infiltration with lymphocytes and polymorphs.
H and E × 85.

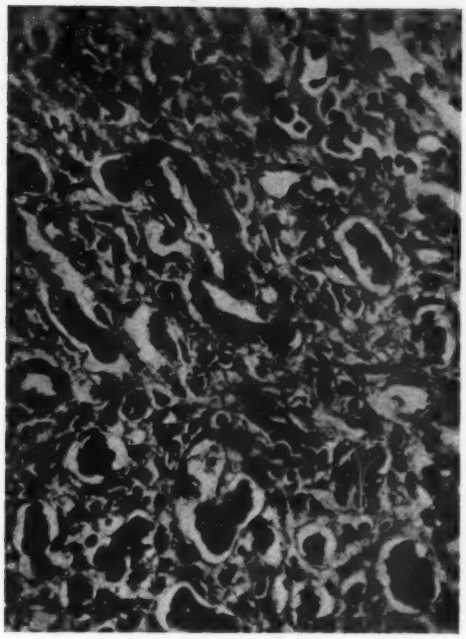

FIG. 2—Liver of Case III. Numerous proliferated bile ducts are seen in the meshes of dense cellular fibrous tissue.
H and E × 300

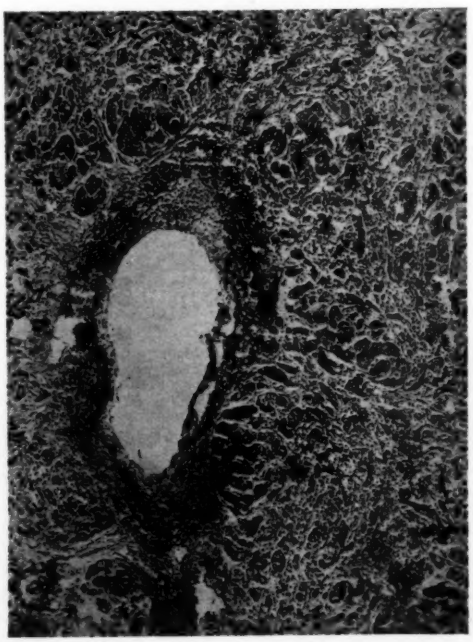

FIG. 3—Liver of Case VI. A large branch of the hepatic vein showing thickening of the wall. The connective tissue of the intima is swollen and has caused a narrowing of the lumen of the vein. Interstitial type of fibrosis is seen in the surrounding area.
Azan × 70

FIG. 4—Liver of Case VII. A large hepatic vein showing diffuse inflammatory cell infiltration of the wall. The parenchyma around the vessel has mostly disappeared and has been replaced by fibrous tissue.
H and E × 80

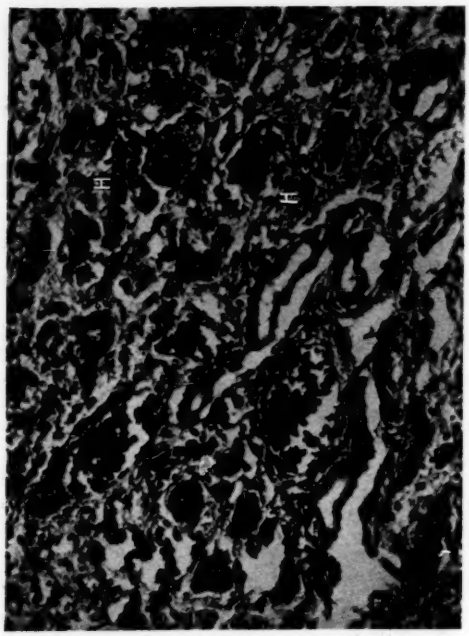

FIG. 5—Liver of Case VIII. Showing moderate proliferation of biliary canaliculi in a dense network of fibrous tissue. H—Islands of persistent haemopoiesis.

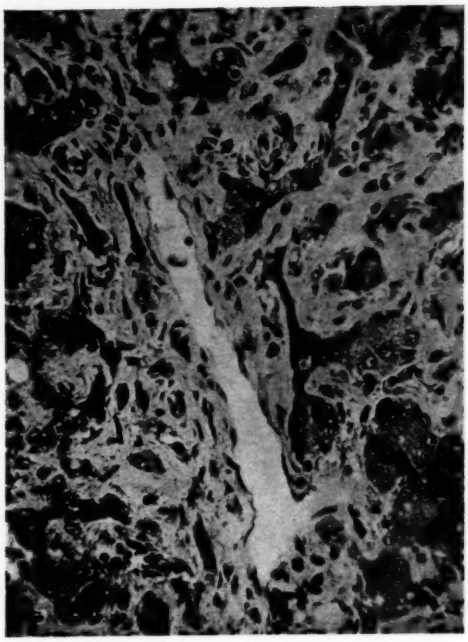

FIG. 6—Liver of Case IX showing the longitudinal section of a central vein with marked thickening of its wall. The parenchyma around replaced by dense fibrous tissue hepatic cords and attenuated.
H and E × 275

FIG. 7—Liver of Case X. Highly cellular fibrous tissue is seen to extend from the thickened wall of a central vein, and to permeate between hepatic cords. The picture is characteristic of interstitial cirrhosis.
Azan × 300

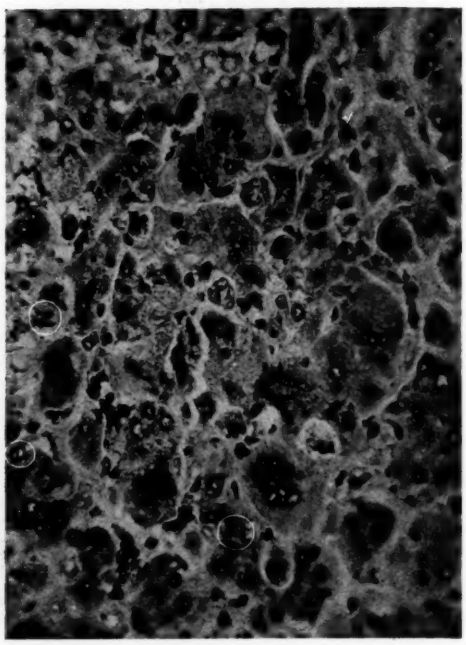

FIG. 8—Liver of Case XVI with congenital obliteration of bile duct. Numerous multinucleated liver cells are seen. B. Inspissated bile in the lumen of the hepatic cords. N. Necrosis of parenchymal cells.
H and E × 300

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that description of the histological findings in the other five cases of infantile biliary cirrhosis from India is not necessary.

Case 7—J.C., Male infant, aged 5 weeks.

LIVER: *Macroscopic appearance*—Slightly enlarged, and firm when cut. Projecting from the surface were a number of nodules which corresponded in cut section with regenerating liver tissue. Islands of normal parenchyma were distributed irregularly in a deeply bile stained fibrous matrix. Gall bladder contained a small amount of bile, and the ducts were patent.

Microscopic anatomy—The normal parenchymal architecture is completely deranged by bands of loose highly cellular fibrous tissue which encircles and isolates pseudolobules of regenerated parenchyma as well as small groups of hepatic cords and single cells. The cytoplasm of the parenchymal cells is granular, vacuolated and invariably shows the presence of bile pigment. Here and there masses of liver cells are undergoing necrosis, their cytoplasm disintegrating into granular bilestained debris and their nuclei showing karyorrhexis and lysis, resulting in the collapse of the sinusoidal reticulum. In these areas there is great proliferation of biliary canaliculi, which vary in their character from structures closely resembling hepatic cords to those of fully developed biliary afferent. Plugs of inspissated bile are found in the hepatic cords as well as in some of the newly formed bile canaliculi. The portal tracts do not show any definite increase in fibrous tissue, or exudate of inflammatory cells.

The epithelium of the bile duct is intact and the lumen patent. The branches of the hepatic vein show slight fibrosis of their wall and there is slight but apparent infiltration of their wall by lymphocytes, endotheloid cells and very few poloymorphs. Coarse granular pigment is observed in the Kupffer cells of the sinusoid, in the histiocytes, and in the isolated liver cells embedded in the fibrous tissue.

Case 8—M.C., Female infant, aged 5 weeks.

Morbid anatomy of the liver—Size normal. It was abnormally hard with sharp edges. Surface smooth, pale yellow in colour, irregularly mottled with red. A few flat nodules of light yellow colour were noticeable on the surface. Moderately tough to cut. Cut section showed the same type of mottling as on the surface; but patches of fibrous tissue were noticed giving the cut section a speckled appearance: A few circular yellow patches suggestive of regenerating liver tissue were present in the cut surface.

Microscopic appearance—Parenchyma: There is extensive necrosis and fatty degeneration of the liver cells throughout the lobule except for a narrow margin of cells around the portal tract. The cytoplasm is eosinophilic, granular and vacuolated, and the nuclei are pyknotic and show karyorrhexis. The sinusoids are distended with red cells, many polymorphs, lymphocytes and monocytes. In those areas where the necrotic process has far advanced, the sinusoids have collapsed through compression by the oedematous necrotic debris and here infiltration with inflammatory cells is well seen. The Kupffer cells are swollen and the nuclei are polymorphic. Many of these are impregnated with bile pigment.

The lymph space of Disse shows oedematous distension with attenuation of the hepatic cord. Portal tracts show increase in fibrous tissue, but fine collagenous strands of connective tissue are seen to extend into the neighbouring lobules along the walls of the sinusoids, evidently due to the transformation of the reticulum fibres into collagenous strands.

The portal vein, hepatic artery and bile duct are normal. There is some infiltration with polymorphs, lymphocytes and eosinophils but this does not bear any relation to the artery, vein or duct, and appears to be part of the general cell mobilization which has affected the whole organ. There is moderate proliferation of biliary canaliculi in the neighbourhood of the portal tract. The cytoplasm and nuclei of these epithelial cells take the stain well.

The sinusoidal bed around the hepatic terminals are also involved in the collagenous transformation of the reticular wall which has resulted in a fine type of interstitial cirrhosis. The hepatic venous tree and its terminal branches show thickening and sclerosis of their wall but the lumen is patent, and widely dilated. The general picture is that of acute liver atrophy in a liver which shows evidence of slowly progressing toxic cirrhosis.

Case 9—J.W. Male infant, aged 6 weeks.

Macroscopic appearance—Liver slightly smaller than normal. Colour deep green, surface finely granular, and consistency firm. It was rather tough to cut and the cut surface suggested fine monolobular cirrhosis. Gall bladder normal. Cystic and common bile duct were patent.

Microscopic appearance—The parenchyma is broken up into narrow tortuous columns and into small groups of cells by cellular and dense connective tissue. The normal lobular pattern is completely lost. Here and there small clumps of cells surrounding the thickened central vein have undergone necrosis, and the transformation of the sinusoids into capillaries can be made out. The parenchymal cells are loaded with coarse and fine granules of greenish yellow bile pigment. Plugs of bile thrombi fill up the potential lumen in the hepatic cords. The outline of the cells is indistinct and the cytoplasm granular and vacuolated. Mitosis of cells and regeneration of lobules of liver cells are absent.

Portal tract: There is moderate increase in the fibrous tissue of the portal tract. The hepatic artery and portal vein are normal. The bile ducts are healthy, their lumen being patent and the lining epithelial cells intact and normal. There is some proliferation of the biliary canaliculi in the region adjacent to the portal tract and a few of them are distended with plugs of inspissated bile.

Kupffer cells show moderate proliferation. Many of them contain fine granules of bile pigment in their cytoplasm, while in others the nuclei are elongated and spindle-shaped and represented a gradual transformation of these cells into fibroblasts.

There is much thickening of the walls of hepatic venous tree with infiltration of inflammatory cells in some branches resulting in considerable narrowing of the lumen. The central veins are also thickened and sclerosed and an endophlebitis is a recognisable feature in most of them.

Case 10—J.W. Male infant, aged 9 weeks.

Morbid anatomy—The liver was small and contracted, dark green in colour and very firm. The diaphragmatic surface was smooth, but the undersurface was nodular. Cut surface showed a uniform fine cirrhosis. Gall bladder and bile ducts were normal.

Histology—The normal architecture of the liver is upset to some extent, by a diffuse interstitial type of fibrosis which spreads in between cords of hepatic cells and along the sinusoids in the form of fine wavy strands and bundles, isolating the parenchymal cells into small and large groups and columns. The parenchymal cells show varying stages of degeneration and necrosis. Many of the parenchymal cells are impregnated with a fine pigment of bile, and in the potential space between the hepatic cords plugs of inspissated bile can be seen. The necrosis is of a diffuse type involving single cells and small groups of cells. Kupffer cells are swollen, proliferated and contain bile pigment.

There is a slight increase of fibrous tissue in the portal tract. The artery, vein and duct are normal. There is no definite proliferation of biliary canaliculi but a few of them are elongated and tortuous probably a natural sequence to the slight increase of fibrous tissue in the sheath. The lumen of the bile ducts is patent and there is no desquamation of the epithelial cells nor is there any pericholangitis.

There is thickening and sclerosis of the hepatic venous tree. Central veins show great fibrosis of their wall, from which extend outward many bundles of fibrous tissue. The larger branches of the hepatic veins show a definite inflammatory infiltration of their walls. The capsule is moderately thickened.

Case 11—C.T. Female infant, aged 7 weeks.

Morphology—The liver was enlarged slightly, coloured dark green with a smooth surface. Cut easily. Gall bladder contained thick dark green bile. Bile ducts were patent.

Histology—The obvious change in the liver is an early interstitial increase of fibrous tissue which spreads from the portal tracts and hepatic veins into the lobule. The cells of the parenchyma show degenerative changes. Their cytoplasm

is deeply pigmented with bile, and their nuclei are irregular in shape and distribution and has affected single cells and isolated cords; but these patches of necrosis seem to bear a closer relationship to the hepatic venous tree and its terminals than to the portal tract.

Portal tracts show a slight increase of fibrous tissue of a cellular character. The hepatic artery and the portal vein are normal. There is a definite but not marked, proliferation of bile ducts. The lumen of the ducts are patent, and there is no inflammatory cell infiltration.

Hepatic venous tree shows a moderate thickening of its wall, and this change has affected the hepatic terminals (central veins) as well. Narrow bands of fibrous tissue can be seen to proceed from the central vein into the surrounding tissue. In the larger branches of the hepatic vein there is a slight round cell infiltration of the wall.

The Kupffer cells are immensely swollen, polymorphic, and are stained greenish yellow with bile.

Case 12—M.C. Female infant, aged 10 months.

Macroscopic appearance—The liver was smaller than average, surface nodular, and of a light yellowish brown colour. It was tough to cut and on the surface could be seen numerous firm nodules separated by fibrous tissue. Gall bladder and ducts were normal.

Microscopic appearance—Narrow bands of fibrous tissue extending from portal tract to portal tract has divided the parenchyma into islands of varying sizes. Extensive fatty change has affected most of the liver cells throughout the lobule. The cytoplasm and nuclei are well stained. There are no areas of necrosis. No hyaline change recorded by Mallory as being characteristic of portal cirrhosis can be seen in the neighbourhood of the Glissons' sheath.

Portal tract: There is a slight increase of fibrous tissue in the portal tract, and this extends beyond, the capsule to link up with the adjacent portal tracts. The resulting picture is that of a multilobular cirrhosis. The walls of the portal veins are relaxed and the lumen is distended with red cells. There is no sclerosis of the portal vein or hepatic artery. The bile ducts are patent and healthy. Proliferation of the bile ducts is slight. A few inflammatory cells can be observed in the portal tract and in the parenchyma abutting on it. Islands of regenerating liver cells are scarce, but a few such islands containing multi-nucleated liver cells and cells showing mitosis are seen.

The sinusoids are collapsed and empty.

The Kupffer cells are impregnated with finely granular bile pigment.

Hepatic venous tree shows no thickening of the coats and there is no inflammatory cell infiltration.

Case 13—E.M. Female infant, aged 3 months.

Morphology—The liver was greatly enlarged, light yellowish green in colour with a finely nodular surface. It had a firm consistency, was tough to cut having a sharp edge, and the cut surface suggested a monolobular cirrhosis. Gall bladder was healthy and contained bile. There was no obvious obstruction in the bile ducts.

Histology—Loose cellular fibrous tissue extending from the portal tract has encircled masses of liver cells, isolating them into lobules. There is some invasion of the lobules by fine strands of collagen fibres; but it is nowhere so extensive as to distort the parenchymal pattern. Most of the liver cells show marked fatty degeneration, a few are necrotic. Plugs of bile thrombi are seen in between the hepatic cords. A few of the liver cells and Kupffer cells are loaded with bile pigment.

Portal tract: There is moderate increase of fibrous tissue of a spongy and cellular type in the Glisson's capsule. It extends from each portal tract to the adjacent ones in narrow bands in which are numerous proliferated biliary canaliculi. Lymphocytic infiltration in these fibrous bands is slight. The artery, vein and duct are normal. There is no thickening or sclerosis of the coats of vessels. The lumen of the bile ducts is patent; but many of the newly-formed biliary canaliculi contain inspissated bile. The hepatic veins, and the central veins do not show any abnormal changes. There is no phlebosclerosis nor endophlebitis.

Case 14—J.N. Female infant, aged 14 weeks.

Macroscopic appearance—The liver was much enlarged, greenish yellow in colour, with a finely granular surface. Its consistency was firmer than normal, cut with resistance and the cut surface indicated a sligh increase of fibrous tissue. A few nodules of yellow liver substance stood out clearly. Gall bladder was normal and contained bile. The ducts were patent.

Microscopic appearance—The parenchyma is oedematous with great distension of the lymph space of Disse, and collapse of the sinusoids. Many of the cells appear rather foamy and the differentiation between individual cells is more marked than normal. Most of the nuclei are well stained, but here and there some of them show karyorrhexis and lysis. An occasional bile thrombus is seen in some of the hepatic cords. A few widely distributed foci of haemopoiesis are revealed on close observation.

Glisson's Sheath: There is a slight increase of fibrous tissue of a loose and vascular character with scanty round cell infiltration. The arteries, veins and ducts appear normal.

The hepatic vein shows no definite change of the wall and the central veins are normal.

The notable feature of this case is the great distension of the lymph space of Disse, collapse of the sinusoid and the change of the reticulum of the sinusoids to collagen as observed with specific stain.

Case 15—A.W. Male infant, infant, aged 3 weeks.

Morphology—Size normal. Bright yellow in colour with red mottling. Appeared to be markedly fatty.

Histology—There is extreme fatty degeneration of the parenchymal cells. The architecture of the liver is well preserved. The fatty change has involved all the parenchymal cells and is of uniform distribution. No areas of necrosis or round cell infiltration are noted. The cytoplasm and nuclei are well stained. The portal tracts show a great increase in fibrous tissue. This increase is chiefly periductal, and follows the ramifications of the proliferated biliary canaliculi. A fair number of lymphocytes, polymorphonuclears, eosinophiles and plasma cells can be made out in the sclerosed periductal fibrous tissue, and in the cellular fibrous tissue following the track of the proliferated biliary afferents. The portal veins show no abnormal change, but some of the hepatic arteries show an adventitial thickening. There is a slight thickening of most of the hepatic terminals and a periarteritis with great narrowing of the lumen of hepatic arteries. There is just a suggestion of collagenous transformation of the sinusoidal reticulum fibres at the centre of some lobules. This is probably an early case of cholangitis lenta described by Naunyn and St. Klein; where there is diffuse pericholangitis but where the periductal sclerosis has not yet brought on any biliary stenosis or stagnation of bile.

Case 16—T.P. Male child, aged 8 months.

Morphology—The liver slightly enlarged. Bile stained to a deep green colour. Surface coarsely granular. Section showed dense fibrosis in a close net work. Gall bladder was absent. Only a mass of fibrous tissue was seen lying at the posterior end of the gall bladder fossa. There was no common bile duct. The condition was congenital obliteration of the biliary passages.

Histology—The structure of the liver is not upset to any remarkable extent. The central veins are patent, and there is no necrosis at the centre of the lobules; but numerous liver cells scattered throughout the lobule show icteric necrosis. Their cytoplasm is granular, has taken the greenish yellow tinge of bile, and their nuclei have disappeared. This wide-spread necrosis of isolated hepatic cells in the lobule has resulted in a certain amount of interstitial or intercellular fibrosis. There are numerous giant liver cells resembling foreign body giant cells with ten or more nuclei in them. No mitosis is seen. Wherever there is necrosis of cells polymorphonuclear leucocytes are much in evidence. Portal tracts

show a great increase of fibrous tissue, which has resulted in marked narrowing of the lumen of the portal vein. The absence of normal bile ducts in the Glisson's sheath inspite of the enormous increase of proliferated biliary canaliculi is noteworthy. Here and there bands of fibrous tissue bridge across adjacent portal tracts destroying the normal architecture of the parenchyma to some extent. The specific connective tissue stain demonstrates the compact bundles of fibrous tissue irregularly disposed in the portal tract, from which delicate strands of connective tissue permeate into the neighbouring lobules along the course of the sinusoids. There is periarteritis and narrowing of the lumen of the hepatic artery.

No alteration is seen in the hepatic venous tree. There is no thickening of its branches, nor is there any increase of fibrous tissue in the adjacent region.

There is increase of biliary canaliculi in the portal tract. A few are branched and tortuous showing aneurysmal dilatations plugged with inspissated bile. It is apparent that they are in direct communication with the hepatic cord which drains the bile into them but not with the bile duct.

The Kupffer cells are swollen and are packed with bile pigment.

The clinical and histopathological findings in these cases are shown in the table given below:

TABLE SHOWING A SUMMARY OF THE CLINICAL AND HISTOPATHOLOGICAL FINDINGS IN SIXTEEN CASES OF CIRRHOSIS OF THE LIVER IN INFANTS

Name and Case No.	*Age in months at autopsy.*	*Family history*	*Diet*	*Clinical history*	*Type of cirrhosis*
V.A. (I)* 1	24	Not available	Not available	Clay coloured stools, anaemia, and oedema of lower extremity	Toxic cirrhosis
A. (I) II	36	Not available	Not available	Not available	Toxic cirrhosis with pericholangitis.
B.S. (I) III	18	4th child to the mother. The 1st 3 had also died of infantile biliary cirrhosis. Children by the 1st wife alive and well.	Mother's milk for 6 months supplemented with cow's milk from 3rd month and with rice from 12th month.	Not available	Toxic cirrhosis
B.L. (I) IV	7	10th child in the family. All the other children heathy.	Mother's milk for 6 months, later supplemented with cow's milk.	Anaemia and leucocytosis, culture of ascitic fluid sterile.	Toxic cirrhosis
B.V. (I) V.	16	All the other children heathy.	Not available	Not available	Toxic cirrhosis
P. (I) VI	20	Not available	Not available	Not available	Toxic cirrhosis
J.C. (E)** VII	1¼	The younger sister died of the same disease later.	Cow's milk and sister Lauara's food.	Commencing peritonitis.	Toxic cirrhosis
M.C. (E) VIII	5	The elder brother died of the same disease.	Breast-fed for 9 weeks. Later, supplemented with Virol and Lactic acid milk.	Changed from breast because not gaining weight. Gained rapidly on change to lactic acid milk.	Acute liver atrophy superimposed in slowly progressing Toxic cirrhosis.
J.W.I. (E) IX	1½	8 children. One died of convulsions at 6 weeks. One of cirrhosis at 10 weeks.	Not available	Not available	Toxic cirrhosis
J.W. II (E) X	2½	8 children: One died of convulsions at 6 weeks and one died of cirrhosis at 6 weeks.	On breast for a few days only. Then dilute milk.	Motion clay coloured and green. Some oedema of legs.	Toxic cirrhosis
C.T. (E) XI	1¾	Not available	Cow's milk	Bleeding from umbilicus when cord was separated.	Toxic cirrhosis
M.O'N. (E) XII	10	Not available	Mother's milk for 1 month. Later artificial feeding.	Clinical, biochemical and X-ray evidence of active rickets. Jaundice at six months.	Portal cirrhosis
E.M. (E) XIII	3	8 children alive. One died of tuberculous meningitis and one of broncho-pneumonia.	Artificial	Glycosuria for 14 days before death.	Portal cirrhosis
J.N. (E) XIV	3½	5 children. 2 died during infancy.	Breast fed	Urine bile stained. Green motions for 1 week.	Serous hepatitis
W.A. (E) XV	¾	2nd child died 4 years ago at birth.	Breast fed	Blood culture sterile. Diarrhoea for 7 days.	Early biliary cirrhosis of cholangitic type.
T.P. (E) XVI	8	First child	Breast fed for a few days. Later cow's milk and Sister Laura's food.	Motions clay coloured from birth.	Cirrhosis due to congenital obliteration of bile ducts. Cholostatic biliary cirrhosis.

*I = Cases from India. **E = Cases from Edinburgh.

COMMENT

After a study of the histopathology of these sixteen cases it is found that they can be classified under five different heads depending on the similarity of features in each group of cases. It was made certain from the report on clinical investigations of these cases as well as from the post mortem findings that syphilis can be definitely excluded as an etiological factor. Infection with micro-organisms is also ruled out as all the sections except two, cases 9 and 13, for which paraffin blocks were not available were stained and examined for organisms with negative results.

Type I comprising the largest number of cases (*vide* Cases 1 to 11) has the following features:

1. Inflammatory cell infiltration of the larger divisions of the hepatic veins.

2. Fibrous thickening of the hepatic veins and their terminals.

3. Intercellular, or interstitial and annular type of fibrosis.

4. Proliferation of biliary canaliculi.

5. Bile stasis.

6. Necrosis and regeneration of the parenchyma.

Type II—Cases 12 and 13 fall under this head and the similarity of features are:

1. Extension of fibrous tissue from portal tracts to encircle large masses of liver cells.

2. Absence of noticeable change in the wall of the vessels.

3. Absence of inflammatory reaction in the bile duct.

4. No apparent necrosis of liver cells.

5. Marked fatty degeneration of cells.

The histopathological picture of these two cases are typical of early Laennec's cirrhosis before vascular changes have set in. All aspects of the histology of this type of cirrhosis have been so well studied and clarified that it does not require any elaboration.

Type III has the following characteristic features (*vide* Case 14):

1. Oedematous distension of the lymph space of Disse.

2. Collapse of the sinusoids and attenuation of the hepatic cords.

3. Loosening of the cells in the cord, resulting in breaking up of the trabecula.

4. Early collagenous transformation of the reticulum of the sinusoids.

This is an example of serous hepatitis described by Rossle and Eppinger.

Type IV (*vide* Case 15). This case is an early biliary cirrhosis of the cholangitic type. The chief changes in this liver were:

1. Periductal inflammatory cell infiltration.

2. Periductal fibrosis.

3. Periarteritis with considerable narrowing of the lumen.

4. Periphlebitis of the portal vein.

5. Marked fatty change in the parenchyma.

The histology is characteristic of the precirrhotic stage of chronic cholangitis described by St. Klein and Naunyn, and reported by Rossle. Preservation of architectural pattern, increase of fibrous tissue in the portal tracts, and periductal inflammatory cell infiltration are the outstanding features.

Type V (*vide* Case 16). This was a definite case of congenital obliteration of bile ducts showing:

1. Increase of fibrous tissue in the Glissons' sheath and between the hepatic cords to some extent.

2. Obliteration of the lumen of bile ducts.

3. Absence of periductal inflammatory cell infiltration.

4. Icteric necrosis of liver cells.

5. Periarteritis and periphlebitis of the portal vein.

There was naked eye and microscopic evidence of obliteration of bile ducts of non-inflammatory origin.

Of these five types the first one possesses histological features which are common to the six cases of infantile cirrhosis of India as well as to five cases from Edinburgh. Five of eleven cases in this type showed a definite familial incidence. Experiments on placental permeability (A. Edwin Sundareson, 1942) prove that a cirrhogenic toxin can pass through the placental barrier, and injure the liver of the foetus. It also passes through the mammary secretion and causes necrosis of the liver of the sucklings in the absence of a protective factor in the diet of the mother (Sundareson, 1947).

It was mentioned before, that in this group of cases, the possibility of an infection in the liver or a syphilitic cirrhosis was excluded. Liver has a remarkable resistance in infection and the role played by the well-developed system of reticulo-endothelial cells in combating infection cannot be over-estimated, but the rich blood supply which acts as a deterrent to infection is probably the very factor that makes the liver susceptible to toxins of various types. From the work of Starling (1894) it is known that the capillaries of the liver and intestine are normally permeable to some proteins. Subsequent work by Sabin and Doan (1926) and by Stillwell (1926) show that the capillaries of the liver are normally much more permeable to dissolved substances of a colloid nature than those of other organs. This permeability of the endothelium of the sinusoids to molecules of greater dimension and

the comparatively sluggish circulation in the liver are factors that place the liver more vulnerable to toxins in circulation than any other organ in the body. Liver possesses a detoxicating action on injurious agents and it is also the clearing house for products of absorption in the intestine. Since the capillaries of the intestine are equally permeable to substances of a colloid nature it is probable that the toxin is an agent absorbed in the alimentary canal. The danger of naturally occurring toxins being absorbed through the intestine and damaging the liver must not be overlooked. Toxic cirrhosis of the liver due to ingestion of cinchophen (Weir and Comfort, 1933 and Kramer, 1934) hydrocin (Ingham, 1933), senecionine (Davidson, 1935) and copper (Mallory, Parker and Nye, 1921) have been reported. It is interesting to note that wheat grown in certain soil containing selenium absorbed enough of the element to produce pathological changes in the liver of the livestock fed on it. (Franke, 1934).

From the study of "The relation between Infantile Cirrhosis of the liver and a diet of polished rice" (Sundareson, 1947) it was found that the diet of the people in those areas where the disease occurred consisted chiefly of polished rice and vegetables and lacked in nucleic acid and proteins. Most of them abstained from taking meat, and the six cases of infantile cirrhosis from India included in the present study are from families of vegetarians.

It is safe to conclude that two factors are involved in the production of necrosis of the parenchymal cells of the liver and the evolution of cirrhosis. One is the protective factor in the diet, in the absence of which a second factor, a toxin probably absorbed from the intestinal tract causes degenerative changes and necrosis of the liver cells. From the experiments of Gyorgy and Goldblatt (1929) and of Rich and Hamilton (1940) it is assumed that it is a toxin normally absorbed from the intestinal tract and detoxicated in the liver in the presence of the protective factor. In the absence of this protective factor, necrosis and later cirrhosis results.

It is possible that in these cases of infantile cirrhosis of the liver, especially in those with a familial tendency, the etiological factors are either an absence of the protective factor in the form of nucleic acid and purine bases in the diet of the mother, or a faulty digestion and failure of absorption of these substances in the mother or infant, or an abnormal metabolism with an inability to utilize absorbed material.

Summary

A comparative histopathological study of six cases of "Infantile Cirrhosis of the Liver" of India with ten cases of "Cirrhosis of the liver in infants" of Edinburgh is carried out.

The six cases of "Infantile cirrhosis of the liver" of India and five cases of "cirrhosis of the liver from infants" in Edinburgh showed similar histological changes in the liver.

The probable etiological factors which may be responsible for the production of this type of cirrhosis is discussed.

Acknowledgment

The author desires to thank Professor A. Murray Drennan for his help and guidance in this work, Professor D. Govinda Reddy for his helpful criticism, and Dr. A. R. MacGregor for placing at his disposal all the material necessary for this study from the Royal Edinburgh Hospital for Sick Children.

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SYMPOSIUM ON ANTIBIOTICS

A Symposium on Antibiotics was held at the Scientific Section of XXIV All-India Medical Conference, Bombay, on 28-12-47 with Dr. A. Erulkar as President.

Speakers: Dr. B. B. YODH, Bombay—Antibiotics in General Medicine. Dr. REBELLO, Bombay—Antibiotics in Skin Diseases. Dr. R. V. RAJAM, Madras —Antibiotics in Venereal Diseases.

Antibiotics in General Medicine

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Bombay

The meaning of this word "antibiotic" is against *living material, i.e.,* that which destroys living agents. It refers, however, to substances produced by or derived from living cells, which are capable of destroying other living cells. Even this meaning would include a large number of substances—not only penicillin, streptomycin, tyrocidine, gramicidin, bacteriophage, pyocyanase, chlorophyll, etc., but also other substances such as, lysozyme and even antibodies as these are produced by living cells.

The term actually is used in a restricted sense to denote "antimicrobial" agents produced by living bacteria, yeasts, moulds and other plants.

The first fundamental fact about these agents is that the susceptibility of various organisms to them varies considerably and a proper knowledge of this well-worked out problem of susceptibility is essential. Penicillin, the most important of the group of antibiotics, acts against Gram-positive bacteria generally and destroys some of them as the streptococcus hæmolyticus, some pneumococci and the gonococci easily, spirochætæ pallida, some leptospira, streptobacillus of rat bite fever fairly easily, while the staphylococcus and some streptococci with greater difficulty. The proper dosage and the frequency of administration can only be determined by a detailed knowledge of these susceptibilities.

From the point of view of proper treatment, therefore, isolation or a probable clinical guess of the infecting organism is the first necessary condition.

The next important fact is the quick absorption and equally quick excretion of the drug from the body. The drug acts only as long as it is in close contact with the infecting bacteria. If this contact disappears, the organisms, not killed, grow again and what is of greater importance especially with streptomycin, they become resistant to the action of the drug and grow in spite of its presence unless the concentration is markedly increased by a much larger dosage.

It has also been found that young growing forms are more easily attacked than older degenerated forms.

These facts indicate the paramount importance of keeping a constant level of concentration of the drug in the blood throughout the course of treatment in all severe infections, and in all resistant strains of bacteria. Whenever the nature of infecting organism is not known and when it cannot be isolated, it would be wiser to give the drug in large doses, and at short intervals.

It is permissible to rely on less frequent dosage even when it is large or incorporated in oil for slow absorption only when it is definitely known that the infecting organism is highly susceptible, is easily available for contact with the drug in the body, and the infection is comparatively mild and localised—as for example boils, small abscesses, localised cellulitis, etc.

This method of administration is not permissible if there is evidence of heavy septicæmic infection, infecting organism is unknown or when there is an inaccessible focus, such as osteomyelitis, infective endocarditis, cavernous sinus, thrombosis etc.

Considerable amount of work has been done on modes of administration. The best method of maintaining a continuous concentration is the continuous intravenous drip—the total 12 hourly dose being put in a saline flask at one time. Although there is the drawback of phlebitis at the site of venepuncture and the necessity of constant nursing care, it is the method of choice—at any rate for the first 24 to 48 hours in very heavy infections, and when organisms are not highly susceptible. After this period the mode of administration may be altered.

The next important method is the continuous intramuscular drip and this being somewhat painful, one per cent novocaine 20 c.c. to a pint of solution may be added to relieve the pain. This method is also quite useful for the first few days in heavy infections.

The method of choice, however, is the intermittent intramuscular injection—although a large number of injections are required daily, 12 to 8 or 6 depending on the severity of the infection and sensitivity of the organism. This is slightly painful although well tolerated on the whole.

Majority of workers come back to this mode of administration after trying out various other methods as the most reliable in serious cases. For relief of pain one per cent novocaine ½ to 1 c.c. or local application of ice are useful.

Subcutaneous route is more painful and the absorption more erratic and hence not usually advised. In order to reduce the number of injections, the oral route has been extensively experimented upon. The drug is absorbed from the gastro-intestinal tract, although the acid in the stomach probably destroys some of the drug. This is overcome by neutralisation by alkali or a protein buffer. The drawback, however, is that five times larger dose is required, and every two hours' or three hours' administration is essential. All workers are of the opinion that the oral route should be used only in mild cases and with extremely sensitive organisms, or in the latter part of the treatment of a severe infection to maintain concentration for a longer period.

Attempts at lowering the excretory rate have been made by a simultaneous administration of a competing chemical agent which will be excreted by the tubules and thus prevent the penicillin from being excreted. The sodium salt of para-amino-hippuric acid is used.

Benzoic acid, which is converted by the liver into hippuric acid, orally 20 to 30 minutes before each intramuscular injection is recommended. This may increase the serum levels 4 to 8 fold.

Prolonging absorption is aimed at by injecting the drug dissolved in peanut oil and beeswax. It does so in the majority of cases but the absorption is often irregular and the method is uncertain in severe infections. It should be reserved for mild infections, when the infecting organism is highly sensitive or for prolonging the effect after the acute stage of a severe infection is overcome.

Local treatment—As the drug acts when brought in direct contact with the organism in infected tissues, and even when purulent material is present, local treatment is extremely important. 20,000 to 40,000 units should be introduced in all infected cavities once a day after aspiration till the cavities clear up. This applies to all surface infections as well. Instillation or inhalation of the drug in the bronchial passages through the trachea has been eminently successful in pulmonary affections. Specially constructed aerosols have been used, and are attached to oxygen cylinders. One has used an adrenalin spray and connected one end with the tube from an oxygen cylinder, 50,000 to 100,000 units dissolved in 1 c.c. being used each time.

Not only is there a good local action on the bronchial mucous membrane, but a satisfactory general absorption as well. Intrathecal, intracisternal and even intraventricular administration are indicated in meningitic and cerebral infections when the organisms are sensitive to penicillin.

Newer Antibiotics

As there are several other organisms capable of producing severe infection and not responding to penicillin, search for newer antibiotics continues and a large number of these have been obtained from various sources. Out of these, Streptomycin (discovered in 1944 by Schatz, Burie and Waksman) produced from fluid cultures of Streptomyces griseus (Actinomyces griseus), a micro-organism isolated from the soil by Waksman in 1919, is a notable advance.

Streptomycin—This agent is far more active against Gram-negative and acid-fast bacilli in experimental infections than penicillin. The compound has proved its value in Gram-negative bacillary infections especially in B. coli group (unfortunately not yet proved of much value in the typhoid group of infections), H. influenza infections (especially meningitis produced by this organism in infants), Kleb pneumoniæ infections (or Friedlander's pneumobacillus pneumonias, etc), against B. tuberculosis in acute experimental infections in animals. In human infections by the tubercle bacillus it is still on trial. Some benefit, however, has been noticed in tubercular meningitis in children, acute miliary tuberculosis in children. The drawback is that 4 hourly i.m. injections for from 3 to 6 months are necessary.

There are greater difficulties with Streptomycin administration than with penicillin. All the principles enunciated for penicillin apply to streptomycin except that as the excretion is slower 4 hourly administration may suffice. Resistant strains, however, develop far more frequently with Streptomycin if the concentration is not well maintained and that too for a long period. This is a real drawback in practice with the small quantities now available. The methods of administration are the same as those of penicillin, except that it is not yet used dissolved in peanut oil and beeswax, and is not given, therefore, as a single daily dose.

Tyrothricin—A brief reference to the use of Tyrothricin locally (gramicidin and tyrocidine combined) is necessary. It is available as a cream and used as such or in suspension in distilled water 0·01 mg. to 0·1 mg. per c.c. It is useful in infections by a variety of organisms mostly however of the Gram-positive variety.

Gramicidin S or Soviet gramicidin is another substance discovered in an anaerbic sporulating bacillus of the *B. brevis* type. It is active against both Gram-positive and Gram-negative groups of organism and will be more useful than Tyrothricin when available.

There are still other antibiotics, such as Streptothrian, Clavacin, Notatin, Penicillic acid etc. Chlorophyll is obtained from fresh or dried leaves by extraction with acetone. It is relatively non-toxic by parenteral administration to human beings. It possesses antibacterial activities *in vitro* against many organisms. *In vivo* it is not so strong. But topical applications are valuable in infected wounds, indolent ulcers, bed sores, and also in cavities that are infected. More requires to be still known.

Experimental work suggests that although the sulfa group of drugs are largely replaced by penicillin, streptomycin, etc., a combination has an additive effect and are not contradictory to each other. In all severe infections, therefore, such a combination should be considered. It is not advisable to use both the groups in mild infections, because of the toxicity of the sulfa groups.

In mixed infections, however, the use of penicillin, streptomycin and sulfadiazine or sulphathiazole may be very valuable, each drug attacking a separate group of organisms in such a case.

Duration of treatment—A point of practical importance in the use of antibiotics is the duration of the treatment. To avoid the development of resistant strains and thus a recurrence, the drug should not be stopped too early but continued for 4 days to one week or more in severe infections after the temperature has returned to normal. Early stoppage has done considerable harm in many cases.

In conclusion, it appears that we are on the threshold of getting other antibiotics which may prove to be of greater value and which will be able to act over a wider range of bacterial infections and especially against infections by the acid-fast organisms—and that it will be possible to tackle the problem of tuberculosis more hopefully in the future.

Antibiotics in Skin Diseases

REBELLO

Bombay

From time immemorial, it has been known that some living organisms destroy others or inhibit their growth. Pasteur and Joubert were the first to suggest that this phenomenon of antibiosis might be of use in the treatment of certain infections. The first attempt to apply an antibiotic for the purpose of treatment was made by Emmeric and Loew in 1899. Fleming's discovery has popularised antibiotics in medical therapeutics. The advent of penicillin and its use in staphylococcal and streptococcal infections opened a new field in dermatologic therapeutics. Though antibiotics are now very largely used on patients suffering from skin diseases, we are beginning to realise that antibiotics in dermatologic practice have a very limited use and that, mainly in pyodermas.

The usual antibiotics that have been tried in dermatological practice are penicillin and tyrothricin. Patulin obtained from penicillium patulum, has been tried by me in an ointment base in diseases due to fungi and the results have not been encouraging.

Streptomycin, produced by a strain of Actinomyces griseus, was described by Schatz, Bugie and Waksman in January, 1944. Owing to its limited availability it has not been extensively tried. I have practically no personal experience of streptomycin having used it in only one patient suffering from lupus erythematosus disseminatus, with unsatisfactory results, possibly due to insufficient dosage. In February last O'Leary and others reported the results of a few cases of cutaneous tuberculosis treated by them. They gave the patients one gram per day of a streptomycin salt in an aqueous solution intramuscularly in divided doses. They gave one patient two grams per day but the dose was discontinued because the patient complained of nausea, lassitude and general debility. The total dose ranged from 15 to 128 grams. They treated four cases of scrofuloderma, one of tuberculosis cutis colliquativa, one of tuberculosis miliaris disseminata faciei and two of lupus vulgaris. Those who had scrofuloderma and received the larger doses of streptomycin derived the most benefit. The results were encouraging but not very satisfactory. They considered the treatment inadequate in some of the cases. Their conclusions are that streptomycin although not the ideal agent for the treatment of cutaneous tuberculosis and tuberculides, does offer considerable encouragement because of its therapeutic efficiency in guinea-pigs inoculated with tuberculosis and because of the varying degrees of improvement in human beings. External and topical uses of streptomycin have not received much attention due to the difficulty in getting the antibiotic in sufficient quantities. There are reports that externally applied, streptomycin proved more valuable than older remedies in certain cases. It has been tried successfully in otitis externa and other infections due to Pseudomonas æruginosa or in skin infections caused by colon bacilli.

Dubos in 1939 discovered an alcohol-soluble but water-insoluble substance called Gramicidin obtained from autolysed cultures of an ærobic, motile, spore-forming soil bacillus called Bacillus brevis. Gramicidin is a high active agent against various Gram-positive organisms *in vitro*. Investigations on the chemical nature and purification of this antibiotic agent by Hotchkiss and Dubos showed that it contained a second substance known as Tyrocidine possessing some degree of activity against Gram-negative micro-organisms. These investigators proposed the name Tyrothricin for designating the mixture of these two substances. Tyrothricin being too toxic for parenteral use in human beings, is employed only by topical application in the treatment of localised infections. It is supplied by the Mulford Laboratories of Sharpe and Dohme for topical application as a concentrate in alcoholic solution requiring dilution with sterile distilled water, which gives a cloudy preparation of the compound in colloidal suspension since it is not soluble in water. Saline solution should not be used as it produces a precipitation of the compound and prevents its even distribution in the diluting medium. The usual concentration for topical applications vary from 10 to 50 mgm. per cent. Higher concentrations produce local irritation with pain or discomfort, hyperæmia, and œdema. Tyrothricin is more rapidly active than penicillin or sulphonamides. It has a low sensitizing potential. Tyrothricin has no systemic use, being too toxic for internal administration and hence any sensitization from local use will not interfere if any systemic therapy later becomes necessary. Moreover tyrothricin is stable and its solutions retain long their usefulness. The only apparent drawback is its systemic toxicity. Therefore care should be taken against too great and rapid absorption as is done when using mercurials or phenols as topical applications. Tyrothricin may be useful in certain cases of acne vulgaris, folliculitis, sweat-gland abscesses, infected cysts, other pyodermas and chronic infected ulcers. Sulzberger and another, report that tyrothricin-containing creams and ointments have proved ineffective in their hands.

Among the antibiotics, penicillin is the one that is most largely used in medical therapeutics. As I have said before its use in dermatologic practice is limited, being used chiefly in pyodermas. It is useful in infections due to penicillin-sensitive organisms or when a secondary infection with these organisms complicates the original condition. The majority of skin diseases which yield to penicillin are those due to *staphylococcus aureus* and *streptococcus pyogenes*. It has been found valuable in impetigo vulgaris, impetigo bullosa neonatorum and adultorum, ecthyma, infectious eczematoid dermatitis, burns and wounds, Bockhart's impetigo, sycosis vulgaris, furunculosis, carbuncle, some cases of multiple erythemas, erysipelas and other streptococcal infections, lymphangitis, lymphadenitis, acne conglobata *et* cystica, some cases of dermatitis herpetiformis, erysipeloid, in Vincent's angina, anthrax, syphilis and yaws. It has not been found of any significant value in acne vulgaris, atopic dermatoses, lichen planus, psoriasis, pemphigus vulgaris, all forms of sarcoidosis, all forms of tuberculoderms, in leprosy, lupus erythematosus, in diseases caused by fungi such as microspora, tricophyta, epidermophyta and the monilias, diseases caused by

filter-passing viruses and the coliform group. Some penicillin-insensitive organisms may even destroy penicillin so that in a mixed infection they indirectly protect penicillin-sensitive organisms. Even in cases in which the organism is found sensitive to penicillin at first, when treatment has got to be prolonged the organism may eventually develop a resistance to penicillin.

There are three methods of administration of penicillin in dermatologic practice:—(*i*) as a topical application, (*ii*) parenterally, (*iii*) orally.

Topical Use

As a topical application penicillin may be used as a solution for spraying or for compresses or soaks. The solution is prepared by dissolving 400 to 1000 units of the sodium or calcium salt per millilitre of normal saline or distilled water. The calcium or sodium salt of penicillin may be incorporated in a cream or a water-soluble base or in an ointment in the strength of 400 to 1000 units of the salt to 1 gram of the base.

J. S. Jeffrey's formula for a cream is as follows:—

Arachis oil ..	125 m.l.
Lanette wax ..	60 gms.
Water	275 m.l.

Heat the sterilized oil to 70 degrees centigrade, add the wax; heat the water to between 60 and 65 degrees centigrade. Add the water to the wax and oil with gentle stirring. Maintain a temperature of 65 degrees centigrade for 2 hours in order to sterilise. Store in 100 gm. pots in a refrigerator until the cream is needed.

A formula for a water-soluble base is as follows:—

White floating soap powder	60 gms.
Distilled water ..	100 m.l.
Cold cream (special) ..	267 gms.

The following is the formula for the special cold cream:—

White wax ..	60 gms.
Spermaceti ..	60 gms.
Hydrous wool fat ..	25 gms.
Cotton seed oil ..	260 m.l.
Sodium borate ..	5 gms.
Distilled water ..	95 m.l.

I have found the following ointment most easy to prepare and most convenient, with the added advantage that the efficacy of the penicillin is preserved for some months without the use of a refrigerator.

Liquid paraffin ..	2 m.l.
Eucerin	100 gms.
Petrolatum album ..	100 gms.

Spencer, Bishop and Ricks recommend a non-greasy tragacanth and glycerine-jelly base. Whatever base is used, the penicillin solution should be added under sterile conditions immediately before it is issued.

The solution and the creams that are made with water have to be kept in a refrigerator to safeguard the activity of the penicillin. The stability of penicillin in aqueous solution is conditioned by temperature and pH. At pH 6·5, or when buffered at that pH, solutions are at their maximum stability. Stock solutions should be stored in a refrigerator at 5 degrees centigrade when they may be reasonably expected to remain stable for one week without requiring re-standardizing. Certain antiseptics are useful adjuncts in aqueous preparations of penicillin to inhibit the development of micro-organisms insensitive to penicillin. Recommended for this purpose are chlorocresol 0·1 per cent, phenoxetol and p-chlorophenol and chlorobutol.

The advantages of local application are:—(*i*) A much higher concentration can be brought to the required site than is possible by systemic injections. (*ii*) There is great economy in penicillin. (*iii*) The treatment can be carried out by the patient himself.

The disadvantages of local application are:—(*i*) The drug is useless if it cannot reach the organisms —because they are too deeply situated as in boils, carbuncles, anthrax and erysipeloid. (*ii*) Occasionally the skin is irritated by either the penicillin itself or an impurity in it or in the constituent of the base in which it is applied. Solutions made in physiological saline irritate some skins due to the deposit of common salt.

Spraying should be done three or four times daily. Treatment by spraying is useful in hospitals, as a large number of patients can be treated without risk of cross infection. It is cheaper. There is no chance of irritation from the base as with a cream. The principal drawback is that the spray apparatus is expensive and tends to become choked and broken. Penicillin deteriorates more quickly in solution than it does in creams and ointments. Spray is not so convenient for individual use.

When prescribing an ointment to a patient, the following instructions should be given:

1. Sterilize the blade of a table-knife by holding it in boiling water for three minutes and allow it to cool.

2. On the knife-blade, take sufficient cream from the jar for only one application, and immediately screw on the lid of the jar.

3. Transfer the cream from the knife to the affected area with a clean finger and smear it evenly on the surface.

4. The cream should be applied twice daily, morning and evening.

5. Never put any cream back into the jar.

Parenteral Use

Parenterally the crystalline sodium salt of penicillin is dissolved in normal saline or distilled water and injected intramuscularly every three hours. The individual adult dose may vary from 20,000 units to 50,000 units. It may also be injected in one or two

doses during the 24 hours. In this case the calcium salt of penicillin in an oil and beeswax base should be injected. The dose varies from 100,000 units to 300,000 units. For sometime now I have been treating patients with one or two large doses of the crystalline sodium salt of penicillin dissolved in normal saline. I have been employing doses ranging from 200,000 units to 500,000 units dissolved in 2 c.c. to 3 c.c. of normal saline.

Oral Use

Orally penicillin-calcium tablets specially prepared for oral use may be tried when it is not possible to give the injections. The tablets contain either 25,000 units or 50,000 units. They may be given in doses of 1, 2 or more tablets at a time, every 2, 3, or 4 hours.

Before treating any dermatological condition with penicillin, the medical attendant should satisfy himself that the condition is produced by a penicillin-sensitive organism or the primary disease is complicated by a penicillin-sensitive organism. Laboratory control methods would be a useful guide. When it is not possible for one reason or another to have laboratory aid, the physician should be guided by his knowledge and experience. In treating superficial pyodermas like impetigo, ecthyma, infectious eczematoid dermatitis, Bockhart's impetigo, sycosis vulgaris or a superficial pyoderma as a complication of other dermatoses, one would resort to topical applications of penicillin. If the condition is acute, exudative and localised, penicillin compresses or soaks would be preferable. The compress should be changed three or four times. It should be covered with guttapercha or cellophane dressing. If the condition is acute, exudative and distributed in different parts of the body, it would be advisable to use a penicillin spray three or four times a day. In bullous impetigo the tops of bullæ would have to be snipped and then the spraying done. In some cases the surface of the skin may be macerated or an oozing surface may be covered with scabs. The macerated skin or scabs should be removed and the skin cleansed with soaks of 1 in 9000 potassium permanganate solution each day before spraying or putting on the compresses. If the condition is subacute or chronic a cream or ointment would be preferable. Ambulatory patients prefer spraying in the day and an ointment at night. If there is no change at all in the condition in 5 or 6 days, it is better to stop the treatment. If the condition is better, the treatment should be continued for five days after involution in cases of simple pyoderma, upto two weeks in cases of slowly clearing or relapsing infections. Contact dermatitis sometimes occurs after four to five days of wet dressing or six to ten days of ointment therapy. This could be minimised by discontinuing the topical penicillin therapy for one or two days after four days' use of wet dressings or six days of application of ointment. During these two days I would recommend liniment calaminæ in an acute condition and a zinc paste in a chronic condition. If the eruption is very extensive or generalised, besides local treatment penicillin should be given parenterally and if that is not possible, orally. In deep pyodermas like boils, hidradenitis, carbuncle, cellulitis, lymphangitis and lymphadenitis due to penicillin-sensitive organisms, penicillin should be given parenterally in doses ranging from 20,000 units to 50,000 units every three hours or in massive doses once or twice daily. The injections may be continued for 5 to 7 days or sometime more. In boils and hidradenitis, penicillin may be sprayed over the lesions and around as a preventive. I have treated a good number of cases of cellulitis, lymphangitis and boils with single massive doses of penicillin parenterally daily. In general the results have been very good. There have been relapses in cases of boils. When there are relapses it is imperative to find the cause and eliminate it. In the treatment of sycosis vulgaris of long-standing, you may be disappointed because of the relapses. Improvement of the general health of the patient is to be aimed at; no shaving of beard is to be allowed and clipping the hair instead, would help the patient greatly.

Reactions to Penicillin

I. EPIDERMAL REACTIONS:

(1) *Contact dermatitis*—Cohen and Pfaff have reported that 0·95 per cent of normal patients, who do not give a history of having used penicillin previously gave positive reactions to patch tests. According to the laws of dermatologic allergy this would indicate that a small percentage of the general public have been sensitized by some previous fungus infection and can be expected to react when penicillin is first applied to their skin. Penicillin in the strength usually applied in solutions or in ointments is not a primary cutaneous irritant. It should not in theory produce contact dermatitis when applied to the skin which has not been sensitized by previous applications of penicillin or by some other fungus. Pringle reports a 20 per cent incidence of dermatitis resulting from the local application of penicillin, particularly on the face. The percentage of dermatitis is considerably less when used in areas other than the face. It would be advisable to do patch tests before using the ointment over large areas.

(2) *Contact cheilitis, stomatitis and conjunctivitis.*

II. DERMAL TYPES OF REACTION:

(1) The commonest is *urticaria.* Occasionally there may be severe urticaria associated with nausea, fever and painful, swollen joints as seen in serum sickness.

(2) *Angio-neurotic œdema.*

(3) *Toxic macular or scarlatiniform eruptions* may occur within the first few days after injections of penicillin.

(4) *Macules, papules and nodules of the erythema multiforme and nodosum type.*

(5) *Phytid type of reactions* may occur after injections of penicillin. I have seen this happen a few times, a few hours after the injection of penicillin. The distribution is usually on the hands and feet and the eruption is vesicular with severe pruritis.

(6) *Bullous eruptions* rarely occur.

III. COMBINED DERMAL AND EPIDERMAL REACTIONS have been observed by me.

Sensitization may occur by topical application of penicillin or when taken orally or given parenterally. The most frequent reactions are urticaria and contact dermatitis. I have treated a good number of cases of syphilis and gonorrhœa with penicillin and only once have I seen a dermal reaction, in a case of gonorrhœa. Whilst in dermatologic cases, whether the penicillin was used topically, orally or parenterally, at least 20 per cent of the patients showed skin reactions. Though penicillin used topically is a useful drug in superficial pyodermas some of these could be treated almost as efficiently with the older remedies without the risk of contact dermatitis and the higher cost the former entails. In deep pyodermas penicillin has a definite place.

In conclusion I have to state that the greatest and most common dermatologic therapeutic problems have not been solved by penicillin.

Antibiotics in Venereal Diseases

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With the time allotted to me I wish to confine my observations to the role of antibiotics in the treatment of the two principal venereal diseases, syphilis and gonorrhœa. Among the antibiotics penicillin is the one drug which has been extensively used in the treatment of these diseases. Most of the knowledge we have acquired regarding penicillin therapy of syphilis and gonorrhœa comes from one country, the U.S.A., where a nationwide, organised co-operative study on penicillin in its chemical, pharmacological, experimental and therapeutic aspects has been in progress since 1943.

Certain broad general statements tentative in character may safely be made from the information available at present.

1. Commercial penicillin seems to be superior to any other compound previously available in its curative effect in syphilis and gonorrhœa.

2. It is by far the least toxic of all anti-syphilitic and anti-gonococcal drugs.

3. Commercial penicillin is a mixture of four penicillin fractions, G, F, X and K, and the relative proportions of these fractions used to vary from the product of one manufacturer to that of another and from batch to batch of the same product.

Since July 1946, most of the manufacturers have succeeded in putting up a product containing predominantly penicillin-G, which is most effective against organisms including spirocheta pallida. There is also some evidence that penicillin-X is more effective for gonorrhœa than either commercial penicillin or penicillin-G. In the meantime the research studies in America have been switched over to the evaluation of Crystalline Penicillin-G. It is quite possible in the future to have pure penicillin fractions like G and X for the treatment of syphilis and gonorrhœa separately and the evaluation studies with these pure fractions may upset or modify our existing knowledge about the value of penicillin in syphilis and gonorrhœa. At the present moment most of the evaluation studies are based on the use of commercial penicillin.

GONORRHOEA

The value of penicillin in gonococcal infections was promptly established after the clinical introduction of penicillin in 1943. Since that time, attempts are being made to determine the optimum dosage, the choice of the antibiotic, the method of administration, and the duration of treatment.

In early acute uncomplicated gonorrhœa of either sex, the following schedules have been reported to give a cure rate of more than 90 per cent and have the advantage of shortness of therapy, convenience, minimum discomfort to the patient and eminently suitable for treatment on an ambulatory basis:

1. 200,000 units of sodium penicillin in aqueous or saline solution, administered intramuscularly, in three divided doses of 50,000, 50,000 and 100,000 units in a two hour period.

2. A single injection of 300,000 units of calcium penicillin in oil and wax, administered intramuscularly.

3. A simultaneous injection of 100,000 units of sodium penicillin in water in oil emulsion with 50,000 units in aqueous solution.

4. The oral administration of 600,000 oxford units of buffered calcium penicillin in divided doses, hourly, over a period of seven hours.

Among the schedules, the two hour schedule of three injections of aqueous sodium penicillin is the cheapest, simplest and best suited for institutional outpatient therapy. In a group of 86 patients with acute gonorrhœa, treated by this two hour schedule, at the Venereal Clinic at Madras, and observed over a period of three weeks to a month, a 93 per cent clinical and bacteriological cure was achieved.

Schedules 2 and 3, in which penicillin is incorporated in absorption-delaying-vehicles are more suitable for the private treatment of gonorrhœa than for institutional use. On account of the cost of the drug, the danger of inadequate and irregular self-medication leading to sensitization and penicillin resistance, oral penicillin therapy does not appear to be the preferable method of treatment of gonorrhœa for the present.

In chronic, complicated, metastatic gonococcal infections and in gonococcal vulvo-vaginitis in children, the abbreviated schedules of therapy recommended for acute disease have been found to be unsatisfactory. A larger total dosage of 500,000 to a million units spread out over a longer period of time seems necessary in addition to certain adjuvant treatments like fever therapy and hormone therapy.

In chronic cases with the presence of other organisms, additional measures such as urethrovesicle irrigation, passage of bougies, prostatic massage, oral administration of one of the sulphonamides may be indicated. In the case of women, physical signs of discharge and irritation may persist even after penicillin therapy due to an associated infection with trichomonas vaginalis.

Recently clinicians from America and to a greater extent from Great Britain have been reporting an increasing number of cases of gonorrhœa resistant to penicillin therapy. In our experience, we have encountered penicillin resistant infections in quite a few cases. Is this the writing on the wall that as in the case of sulphonamides, the gonococcus is adapting itself to the antibiotic menace to its perpetuation? Time and further observation alone can tell.

In the meantime, laboratory and clinical studies of streptomycin in gonococcal infections reveal a promising additional weapon against the disease. In a few cases of penicillin-resistant gonorrhœa the administration of streptomycin in 3 to 5 gm. total dosage have been reported to have cured the infections. We have no personal experience of this. Modern scientific medical research is providing one drug after another, first the sulphonamides, then penicillin and thirdly streptomycin in the fight against the elusive gonococcus and one really wonders whether this strict human parasite, famous for its biological opportunism can ever be weeded out of the human population. The possibility of a coincident but potential syphilitic infection in patients treated for gonorrhœa with penicillin should always be borne in mind. Such patients should be watched for any clinical or serological evidence of syphilis for a minimum period of three months.

Syphilis

Penicillin therapy of Syphilis—1. In early syphilis the curative effect of penicillin therapy is directly proportional to the speed with which the diagnosis is made after the infection.

2. Best results are obtained in sero-negative primary syphilis with a reported cure rate of nearly 98 per cent.

3. In sero-positive early syphilis, including secondaries, the percentage of unsatisfactory results following penicillin therapy is still high (about 25 to 30 per cent). Hence it is suggested that in every case of sero-positive early syphilis, a combination of penicillin with other anti-syphilitic drugs, Mapharsen and bismuth should be given. There is evidence, both experimental and clinical that a combination of penicillin with Mapharsen and bismuth or both, may give better results than penicillin alone. A synergistic action is postulated.

4. The recommended dosage of commercial sodium penicillin is 3·6 mega units for sero-negative primary syphilis and 5·4 mega units for sero-positive, primary and secondary syphilis.

5. The incidence of the so-called reinfection or super-infection seems to be six to ten times more frequent following penicillin therapy than with the old standard metal chemotherapy.

Syphilis in Pregnancy—The most spectacular results have been reported in the prevention of prenatal syphilis following penicillin therapy in syphilitic pregnant women, from the two University Clinics, Philadelphia and Baltimore. The prevention or cure rate of 98·4 per cent among the infants born is unequalled by any other form of therapy. In penicillin, the results are equally good, no matter what the duration of pregnancy is at the time of treatment.

In a small number of eight cases of early infectious syphilis in pregnancy, treated by us with penicillin, we were able to confirm the very favourable reports by the American workers. The risk of reaction to either the mother or the infant is almost negligible. The recommended dosage should not be less than 3·6 mega units and not more than 5·4 mega units, administered intramuscularly, in aqueous or saline solution, third hourly, round the clock in single doses, varying from 40,000 to 90,000 units. After treatment the mother should be followed up clinically and serologically, once a month till the time of delivery. After birth the infant must be followed for a minimum period of three months, clinically, serologically and roentgenographically.

Congenital Syphilis—Platou and co-workers from five co-operative university clinics in America, published an instructive study of the results of penicillin therapy in 252 infants with early congenital syphilis. They have reported 73 per cent satisfactory results, 9·1 per cent unsatisfactory results and 17·9 per cent in which the results are classified as uncertain. A mortality rate of 10·7 per cent from all causes is reported among the treated infants. In a group of 59 infants with early congenital syphilis, treated at the Venereal Clinic at Madras, 42 infants were discharged clinically cured with 5 deaths in the hospital. Of the 24 infants who have been followed and been under our observation from periods varying from one month to ten months, 20 are clinically well and 10 of them have been under our observation for more than four months and have achieved serological negativity. The following conclusions may be stated regarding the treatment of congenital syphilis with penicillin:—

1. The recommended dosage of commercial penicillin is 50,000 units per pound of body weight to be administered in 120 equal divided doses during a period of 12 to 15 days.

2. In grossly debilitated marasmic infants, the initial dose should be small of about 500 units gradually stepped up till a maximum of 5,000 units is reached in the course of a week or ten days.

3. Clinical response to the therapy has been uniformly satisfactory but it takes a longer time for the reversal of the serological reaction in early congenital syphilis than in early acquired syphilis.

4. Adequate and expert pediatric care is essential to successful penicillin therapy of congenitally diseased infants.

5. Most of the deaths reported during treatment occurred on the basis of malnutrition, dehydration and intercurrent infections.

In late congenital syphilis, particularly in interstitial keratitis the results of penicillin therapy are disappointing.

Neurosyphilis—Clinical and serological improvement have been reported in varying degrees in all types of neurosyphilis by the parenteral injection of penicillin in spite of the fact that penicillin does not penetrate the C.S.F. in any demonstrable quantity. In asymptomatic neurosyphilis and in acute syphilitic meningitis, the results of penicillin therapy in doses of 3 to 5 mega units have been reported to be excellent.

In paresis, primary optic atrophy, and syphilitic psychosis, penicillin administered concurrently with malaria or other forms of fever is considered superior to penicillin alone.

In tabes, the results of penicillin therapy are disappointing. The recommended total dose of penicillin varies from four to ten million units. Increasing the duration of treatment and multiple courses are suggested to improve the results of short and single course therapy.

Cardiovascular Syphilis—Because of the danger of therapeutic shock and therapeutic paradox this form of syphilis has not been investigated from the point of view of penicillin therapy in the same organised manner as other types of syphilis. In late benign gummatous syphilis of the skin, mucous membranes and bones, the administration of penicillin, three to four million units, has produced rapid healing of the lesions.

The use of sodium penicillin in the treatment of syphilis, requires hospitalization of the patient and so long as it remains an obligatory hospital procedure, it will remain unsuitable and inapplicable for the mass treatment of syphilis.

A number of reports have now appeared from America, indicating that satisfactory results in early syphilis can be obtained with ambulatory treatment, utilising penicillin in oil and wax. The larger series of 802 cases of early syphilis, treated with penicillin in oil and wax has been reported by Thomas, Landy and Cooper of the Bellevue Hospital, New York City. According to them, the treatment of early infectious syphilis with a single daily injection of 600,000 units of penicillin in oil and wax for eight days has proved very satisfactory. In a small series of six patients with early syphilis treated privately by me with a single daily injection of 300,000 units of penicillin in oil and wax for a period of 12 days and observed over a period of six to ten months, the results have been very satisfactory, clinically and serologically. The technical difficulty of administration, due to the high viscosity, the increased incidence of allergic effects and the cost of the drug will militate against its routine use in the treatment of syphilis. American workers, Henry Welch and Romanskey, are now collaborating on an extensive research to prepare penicillin in oil in a comparatively free flowing form and which will be as effective as the old viscid preparations. When the work is completed, liquid preparations of oil and wax may become available for the treatment of syphilis.

From studies on experimental syphilis, it is gathered, that streptomycin is very much less efficacious than penicillin and hence it is possible, that the drug shall have no therapeutic future in syphilis.

In conclusion, it may be said that the treatment of syphilis with the antibiotics particularly penicillin, is in a state of flux and four years is too short a period to assess its value in a disease which is as chronic, relapsing and subtle as syphilis.

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DISCUSSIONS

DR. P. L. DESHMUKH (*Poona*) said:—Speakers before me have repeatedly voiced that penicillin has been grossly abused or misused. While agreeing with them in spirit, I beg to sound a note of dissent on one point. Penicillin is relatively of recent introduction in therapeutics, and I believe that its potentialities are not yet completely explored. So, one can not be too dogmatic about its indications and contra-indications except in a few cases. Laboratory research *in vitro* by itself is not sufficient to decide the fate of a remedy though it may throw a useful light on it. Clinical test alone is capable of giving the final verdict. So, medical practitioners should be encouraged to try a new, safe and potent drug in different diseases and in tried diseases from a different point of view. Thus potentialities. For, in medicine, as we see in the alone it will be possible to reveal the drug in all its world around us, what may be considered as out of order to-day may prove to be the basis of order of the morrow.

This introduction may be considered as an apology for my further remarks. For, though the Plasmodium is known to be insensitive to penicillin, I tried the drug in cases of relapsing malaria with great success. This is how I came to use it in my first case. A lady was brought to me for repeated relapses of malarial fever though she had been liberally treated with injections of quinine, mepacrine tablets and quinine mixture, by her previous medical attendants. I thought of using penicillin in conjunction with the usual anti-malarials and wanted to see if relapses could be checked. I gave intramuscular injections of penicillin two lac units in 5 c.c. normal saline on three consecutive days simultaneously with injection of quinine hydrochlor gr. 6 intramuscularly on the first and third days of penicillin. Mepacrine tablets were continued five days longer at one twice a day. To my surprise I found that the patient did not get a relapse to this day *i.e.*, during about a year. Further cases which I treated on the same line gave uniformly successful results clinically and bacteriologically. I believe the explanation of this success lies in the modern theory about the mechanism of a relapse. According to the modern conception, the Plasmodium is assumed to have two cycles in the human being *viz.*, a corpuscular and an exrta-corpuscular cycle. The latter is also known as the 'reticulo-endothelial' or the 'X' cycle which has been definitely proved in birds. Relapses are explained on the assumption of overflow of parasites in the peripheral blood from the extra-corpuscular cycle. I assume that the usual anti-malarial drugs, which in reality form only the suppressive treatment of malaria, kill the parasites in the peripheral blood, while penicillin has a selective action on the extra-corpuscular cycle of the malarial parasite.

If my observations are corroborated by my colleagues here, a new and very useful vista will be opened for penicillin therapy.

DR. G. COELHO (*Bombay*) said: Adequate facilities for investigation of a case are not available for the general practitioner, hence there is a danger for overprescribing.

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In pediatric use, injections into multiple boils, empyema cavities after aspiration of the pus is a useful procedure. The experience with typhoid fever treated with penicillin alone, 50,000 units every 3 hours for 4 days is not conclusive because of the few cases, so treated, but I am inclined to think that it is beneficial in toxic cases. The clinical results in congenital syphilis treated with a dosage of 75,000 units per pound of weight distributed over 14 days, are superior to those obtained with arsenic, bismuth and mercury. Similar has been my experience with stomatitis. In diphtheria penicillin combined with antitoxin is valuable in toxic conditions, but in all cases of diphtheria the antitoxin should not be forgotten.

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DR. BALDEV SINGH (*Amritsar*) said: It is a recognized fact that the quantity of magnesium ribonucleic acid present in the organism determines the sensitivity of the organism to penicillin. In cases of typhoid fever and Malta fever if antiserum is given along with penicillin the diseases are easily vulnerable to the treatment. This is attributed to the fact that the corresponding organism is able to take a greater quantity of magnesium ribonucleic acid.

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DR. P. N. PRADHAN (*Nagpur*) said: State control of penicillin is necessary. Pharmacology of penicillin is a debatable point in regard to how it precisely acts. If it creates an unsuitable environment for the growth of the invading organism or if it acts on the growth factor, *viz.*, para-amino-benzoic acid or others. This point opens a wide field for the bacteriologist to study, why a particular organism is sensitive to penicillin. It is also important to determine how long it will take for the growth factor once it has been destroyed by penicillin to appear in circulating blood. Single massive dose of penicillin was found useful in a case of bilateral palmar abscess whereas in a case of rheumatic endocarditis, repeated courses of penicillin failed to be effective.

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DR. M. R. CHOLKAR (*Nagpur*) said: Penicillin is effective in breast abscess, with sinus as well as in unopened direct abscess. An article on a few cases of breast abscess treated in the way has appeared in an issue of *Lancet* of 1947.

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L. R. DESHPANDE (*Hyderabad, Dn.*) said that he found good results with penicillin treatment in erythema nodosum, diphtheria, tetanus and typhoid.

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DR. C. N. SHROFF (*Bombay*) also spoke.

BENEFITS OF OPEN AIR IN THE TREATMENT OF TUBERCULOSIS

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In India there are no special hospitals for tuberculosis of bones and joints. The average case is put in plaster of Paris or some sort of splint and treated at home or sent away to his native place. In all civilised countries these cases are treated in special hospitals, far away from crowded cities and entirely in the open air. Foreign domination, poverty and ignorance have so far prevented such treatment from being undertaken in this country. The general surgeon is used to rapid operations and quick cures. He has not developed that patience which is necessary for prolonged, conservative treatment of these diseases. With increasing consciousness for the need of othopaedic surgery, such hospitals however are bound to develop. They require specialists who can devote time and have the patience to look after the same patient for years, if necessary for very little remuneration.

It was Hugh Owen Thomas (1834-91) who realised the value of open air treatment in tuberculosis of bones. He used to insist on his patients being kept outside in the open air, and it was a common sight in his days to see children on their frames lying in the garden or on the street. His nephew, Sir Robert Jones (1858-1933) had the genius to appreciate what cured these cases. He found luckily in Miss Agnes Hunt, one of his patients, an admirable worker, who first started a small hospital. From humble beginnings through the efforts of Sir Robert Jones and Miss Agnes Hunt, that hospital has grown to-day into an institution with 1500 beds devoted mainly to this problem. People from all over the world come to see this experiment and go back convinced about the treatment of tuberculosis of bone in open air.

In Sir Robert Jones' own words "Over twenty years ago, with the help and inspiration of Miss Hunt, the first really open-air hospital was established at Baschurch in Shropshire. Its early days were days of hardship, but never of despair. The hospital was composed of a few sheds in a field, the operating theatre occupied the back kitchen, and obstacles were so frequent and so apparently unsurmountable that they ceased to raise a qualm and became indeed an exhilarating part of the daily routine. Around Miss Hunt gathered a body of enthusiastic young women who became in due course experts in the application of splint and plaster work. But the great lesson of Baschurch was the benefit of exposure to the open air night and day. The second lesson was the importance of efficient orthopaedic training for the nursing and aftercare staff."

Even when tuberculosis affects the rich in this country, the majority of them are put up in plaster of Paris or in a splint and are treated at home in a congested city. In a few months they get disgusted with the plaster and the lying down. Mercer in 1946 in discussing prognosis of tuberculosis of bones and joints in his text book writes: "Reference should be made to the great improvement in prognosis that has attended the efficient sanatorium regime now practically universal in this country". This shows the importance of open air in prognosis of tuberculosis of bones and joints. In these hospitals, besides the open air, there is a peculiar buoyant atmosphere. The psychological effect of seeing a fellow patient going out cured is a tonic which patients at home can never get. The sight of patients at various stages of improvement also helps a new patient considerably in bearing the tedium of lying down.

In an open air hospital these patients are kept in the verandah for twenty-four hours even on the coldest day. All are given both general and local rest of some sort in a plaster cast or a splint. They are given colloidal calcium with vitamin 'D' injection 2 c.c. twice a week and a mixture containing iron and arsenic and glycerophosphates. Tuberculin in very minute doses (1/10,00,000) may also be given to these cases once a week, gradually increasing to 1/10,000. The sedimentation rate is tested as a routine by Westergren's method and shows improvement with the clinical progress. Cod liver oil, calcium, vitamin D, ultra violet therapy are all adjuncts. But often they are used only as primary treatment.

The following cases which were treated in an open-air hospital may prove interesting:

Report of Cases

Case 1—T.C., H, male, aged 45, admitted on 4-5-1944, with quadruplegia of three weeks's duration. He had a temperature of 100°F and his sedimentation rate was 90 m.m. per hour. His lesion was at the fifth and sixth cervical vertebrae with dislocation and his X-ray films showed destruction and decalcification of bones. A Minerva plaster was applied. It took three months to get rid of the paralysis and pyrexia. He steadily improved and was discharged on June 1, 1945 with a support. He took three months' rest at home and since then he is doing full eight hours' duty. His lesion has healed as there is bony fusion of the fifth and sixth cervical vertebrae. His sedimentation rate is now 10 m.m. per hour. The period of convalescence was in my opinion considerably shortened due to treatment in open air.

Case 2—J.F., female aged 39, admitted on 20-9-1944 with lumbar abscess on the left side. It increased in spite of a plaster jacket. Her temperature was 100°F, sedimentation rate 120 m.m. per hour. The abscess was aspirated three times but still it filled up. So the abscess was deliberately opened as advised by Girdlestone (1944). The abscess healed in only five months' time and she was discharged on 15-3-1945 with a belt. This rapid healing of the lumbar abscess was due to deliberate opening and antiseptic dressing along with the open air regime.

Case 3—Master H, aged 11, admitted on 22-6-45 for bilateral tuberculosis of the ankle joints for seven years. He had been treated in various places in Sind and had been advised bilateral amputation of the leg. There were multiple sinuses on the left side and the ankle had swollen to three times its size. X-ray showed decalcification and the normal trabeculations had completely disappeared. The ankle on the right was not as bad as on the left and x'ray examination showed less destruction. His sedimentation rate was 100 m.m. per hour. The patient was having a maximum temperature of 101°F on admission. He was emaciated, anæmic and looked very toxic. It seemed justifiable to amputate both the legs considering the toxicity and anaemia. He was however treated conservatively in the open air clinic and was put up in plaster of Paris upto above the knee. After one year he was looking better and x'ray examination showed that calcification was occurring. Eighteen months after this 2½ years after his admission, the pale anaemic boy had become a dark, healthy adolescent. He had that peculiar dark complexion found in the Koli boys round Versova and Vasai. This change was due mainly to the open air near the sea-side. Recent x'ray films show that trabeculations have returned and calcification is almost normal. He will be discharged when the sinuses heal. The patient is now looking quite healthy and normal.

Case 4—C., female, aged 35, was treated for eighteen months in another hospital. She was admitted on 15-10-1945 with a sinus in the left groin and tuberculous lesion of the second and third lumbar vertebrae. Her temperature was 99·5°F and sedimentation rate was 85 m.m. per hour. The sinus healed in eight months and her temperature came to normal. Today she can walk about with a posterior support. Her sedimentation rate is now 20 m.m. per hour and x'ray examination shows satisfactory sclerosis.

Case 5—S. G., female, aged 21, was admitted on 24-2-1946. On admission she had a swollen left knee joint with sinuses. It was tuberculous in nature and of eighteen months' duration. Her temperature was 100°F maximum. Her sedimentation rate was 80 m.m. per hour. The joint was immobilized in plaster of Paris till February, 1947. She had not improved very much during this time and sinuses still persisted. The temperature however had settled down to normal in three months' time. After February 1947, a Thomas' knee splint was given. The improvement since then has been remarkable and she has put on 20 lbs. weight. In my opinion the Thomas splint immobilises the knee more satisfactorily than a plaster of Paris cast in tuberculous conditions. The muscles relax completely. In a plaster of Paris cast, the muscles can contract and often cause an abscess. Thomas, it may be mentioned here originally used his splint for tuberculosis of the knee. This patient would have required an amputation considering her anaemia, thin wasted appearance and sinuses. I feel that open air conservative treatment saved the limb.

Case 6—R. G., male, aged 47, admitted on 11-12-1947, for tuberculosis of the right ankle joint with three sinuses. He had been advised amputation of the leg but had refused to get it done. On admission his sedimentation rate was 60 m.m. per hour. A crab splint and the usual line of treatment was adopted. The sinuses healed in two months and he improved rapidly. He has been discharged with a walking calipers with which he can walk about. His sedimentation rate is now 15 m.m. per hour. This patient but for the open air hospital, would have lost his leg.

Conclusion

I am personally convinced that the cases mentioned above would not have had such satisfactory results without the treatment in an open air hospital. In the open air hospital referred to above, 61 patients have been treated so far.

Following table shows the number of cases and the sites of tuberculous affection:

Site affected	*Number of patients*
Spine	40
Ankle	8
Hip	6
Knee	2
Sternum	2
Elbow	2
Metatarsal	1
Total	61

Out of the 40 cases of tuberculosis of the spine, 3 left the hospital prematurely, 1 because he could not afford further treatment, 1 due to leprosy and 1 because of language difficulty. 3 were cases in the terminal stage and they died. 1 early case also died from severe anaemia which could not be cured with liver extract injections, iron therapy and blood transfusions. 3 cases had tuberculosis of the lungs and were asked to go to some other hospital. Thus at least 31 patients out of these 40 cases of caries spine benefited by the open air treatment. It is however no good calculating the percentage of results on such a small number of cases. Still, it seems worth stressing that of the cases undergoing treatment when not in extremis, only 1 out of 31 died. This compares favourably with the mortality figures in Liverpool and Oxford (5 per cent immediate mortality).

In conclusion, may I reiterate that the object of this paper is to stress the value of open air hospitals for the treatment of bone and joint tuberculosis and the need for many such hospitals all over India.*

*Read at the XXIV All-India Medical Conference, Bombay, Dec. 1947.

SPECIAL ARTICLE

THE BRITISH PHARMACOPOEIA—1948

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The seventh revision of the British Pharmacopoeia has been published this year, the first having been published in 1864. The British Pharmacopoeia was expected to be revised at intervals of ten years, incorporating established new drugs and modifying, if not weeding out old and less serviceable ones. The last (sixth) was published in 1932. From then to now, no less than seven addenda were issued to take the place of the rightly due 1942 revision, in an attempt to keep up to date the 1942 revision, delayed due to war conditions.

Evolution of the British Pharmacopoeia

It is interesting to study the evolution of pharmacopoeias in general and the British Pharmacopoeia in particular, as the study is just another aspect of progress of medicine.

The first work of its kind published under government authority appears to have been that of Nuremberg in 1543. A passing student, Valerius Cordius showed a collection of medical recipes which he had collected from the writings of eminent medical authorities, to the physicians of the town who impressed by it, urged him to print it for the benefit of the apothecaries. They obtained for his work sanction of the senatus. An earlier work known as "Antidotarium Florentinum" had been published under the authority of the college of medicine of Florence.

Until 1617, drugs and medicines as were in common use were sold in England by the apothecaries and grocers. A row between the grocers and the apothecaries, resulted in the college of physicians in 1618 empowering only the apothecaries to dispense medicines and that according to specifications embodied in a 'Pharmacopoeia' by the college of physicians. This, the first London pharmacopoeia had included mostly the works of Mezue and Nicolaus de Salerno. The compounds employed here were often heterogeneous mixtures of 20 to 70 ingredients. Among others, the ingredients included oyster shell, pearls, crabs' eyes, excrements of human beings, dogs, mice, geese calculi, human skull and moss growing on it (probably the beginnings of penicillin), blind puppies, earthworms, etc. This pharmacopoeia existed till 1721 when under the auspices of Sir Hans Sloane, important alterations were made, deleting many of the aforesaid ridiculous remedies. The tendency to simplicity was carried to a much greater extent later and in 1788 the edition then published purged itself of the heterogeneous hodge-podge of 2,000 years old remedies. The first Edinburgh pharmacopoeia was published in 1699 and the last in 1841. Similarly Ireland had its own, the first being published as late as 1807 and the last in 1850. The preparations contained in the three united kingdom pharmacopoeias were not all of uniform strength and was naturally a source of much inconvenience and danger to the public. In consequence the medical act of 1858, ordained that the General Medical Council should publish a book containing a list of medicines and compounds to be called the British Pharmacopoeia for the whole of the British isles. Hitherto they were published in Latin and the first edition in English appeared in 1864.

A dissatisfaction was felt over this edition as the majority of the compilers were not engaged in the practice of pharmacy and the committee constituted as such was competent rather to decide upon the kind of preparation than upon the method of their manufacture. (We hear today in India the echoes of the dissatisfaction, as India is striving to place pharmacy, drugs and pharmacopoeias in order). The necessity for this element in the construction of a pharmacopoeia is now fully recognised in every country, in most of which pharmaceutical chemists are represented on the committee for the preparation of the legally recognised manuals. National pharmacopoeias under the authority of government now exist in almost all advanced countries.

But the rapid increase in medical, pharmacological and pharmaceutical knowledge renders necessary frequent new editions. Each new edition of a pharmacopoeia requires several years of experimental work for developing suitable formulae and hence the production at intervals of such works as Squire's Companion to the Pharmacopoeia, Martindale's Extra Pharmacopoeia, New and Non-official remedies of the American Medical Association etc., that tend to keep the medicinal preparations abreast of time. With many medical practitioners, the Extra Pharmacopoeia is more the bible than the B.P. or the U.S.A. one. The British Pharmaceutical Codex is published under the authority of Pharmaceutical Society of Great Britain, in which the character and tests of purity of many non-official drugs, their preparations, glandular products, sera vaccines, etc., are given. This work may serve as a guide under the Foods and Drugs Act for the purity and strength of drugs not included in the B.P., and as a standard for the commercial grades of purity of those in the pharmacopoeia which are used for non-medicinal purposes as well.

International Pharmacopoeia

The desirability of a uniform formula for the more important medicaments, is forced by the ever increasing facility for travel, intercommunication and interrelation of nations in many spheres. Attempts have been made by international pharmaceutical and medical conferences to settle the basis on which an international pharmacopoeia could be prepared. But owing to the usual national jealousies and the attempt to include too many preparations (what is soup for the goose is sometimes a poison for the gander) it has not yet materialised. The British Empire by permit-

ting an Indian and a colonial addenda in 1900 made an attempt at unification in a limited sphere. The health organisation of the U.N.O., who knows, may attempt this.

Indian Pharmacopoeia

In 1900 an Indian and colonial addenda were permitted to the fourth revision of 1898. The Government of India edition of 1901 was accordingly published to suit "Indian conditions." Before the compilation of the 1932 edition, the civil research sub-committee on the British Pharmacopoeia suggested, "Where it is desired that official recognition should be given in any part of the empire to any local drugs or local substitutes we suggest that this should be left to the governments concerned, which by means of supplements or addenda, to which they may accord the necessary sanctions, can meet any local requirements or introduce any modification or alteration desired." Accordingly an Indian pharmacopoeial list has been published in 1946. Its utility is yet to be established. It includes in the main several bitters, volatile oils, astringents for which Indian botany and materia medica are famed, malt, extract malt with shark liver oil, derris, pyrethrum, Paris green (insecticides) cobra and viper venoms, pilula aloes et ferri and asafoetida (omitted by the new B.P.) etc.

The British Pharmacopoeia of 1948

The task of compiling the last edition has by no means been an easy one. The committee has been assisted by a clinical committee of 20 members, eight other committees, some of them with several sub-committees. The difficulty was enhanced by the fact that the compilers had to look not to the immediate future, but to 5 or 10 years ahead. It may happen that some preparation on the crest of its popularity finds no mention in the list while another which has virtually been discarded may find a place. The seven addenda from 1932 to 1945 had tended to bridge a wide gap which otherwise would have been felt and tended to keep the 1932 edition reasonably up-to-date, war conditions and rapid therapeutic advances taken note of.

The main interest about the 1948 British pharmacopoeia (due in September this year) is the striking commentary it provides on the great therapeutic advances of the last decade or more. Ostensibly this is evidenced by the size of the new edition which has about 300 pages added to the previous one. About 150 entirely new monographs and about 155 new names have been introduced. It has incorporated new, none the less familiar preparations like 'Cremora', 'Tabella', 'Emulsio' etc. The official injections have been increased from 6 to 84.

As evidence also of its reorientation is the discarding of no less han 145 monographs of the 1932 B.P. Therapeutics, of late, having become a swiftly progressive art *cum* science, agents of questionable, under or objectionable utility have rightly been passed by. Old is not always gold; it sometimes tends to get mouldy and has to be deemed a sold out product. The exit of several drugs are for the reasons such as (1) their utility is not commensurate with their unwanted actions, (2) better substitutes, possibly cheaper are readily available and (3) occasionally one or other is not available or not possible of steady output. The new admissions of drugs are for precisely the reverse reasons *i.e.*, their established use based on known or recognised actions, their ready availability, etc.

In the inclusion of new medicaments, the new B.P. has maintained its traditional cautious conservatism and a considerable time-lag is noticeable between the introduction of new remedies and their final installation in the pharmacopoeia.

Though the Pharmacopoeial Committee was mainly concerned with the laying down of standards of activity, its task of assessing clinical utility has been rendered easy by the labours of institutions like the 'Council of Pharmacy and Chemists' of the American Medical Association or the 'Therapeutic Research Council' of the British Medical Association, that are more concerned with protecting the medical profession and the public against ".....fraud, undesirable secrecy, objectionable advertisements etc., in connection with the medicinal agents" and to assess drugs with reference "....the status of medicinal articles it is importuned to use" by the manufacturer. The pharmacopoeia nevertheless should be the standard for a medical man who should seek its aid on all occasions. How many general practitioners own a pharmacopoeia? The pharmacopoeia also tends to enforce a medical discipline with regards nomenclature, dosage etc. Official names of proprietary preparations are not known to many. Sometimes one comes across a medical man who is shocked that the dispenser had violated his instructions in having given 'Sulphathiazole' when the doctor had prescribed 'Cibazol' as though a poison was substituted. Atebrin is better known than mepacrine and a good few are confused between mepacrine, pamaquin, plasmochin and quinacrine.

A legal difficulty of modern pharmacopoeia is the inclusion in some of them of synthetic chemical remedies, the process for preparing which have been patented and the substances are sold under the trade mark names such as cibazol The scientific chemical name is often long and unwieldy and the physician by naming the drug by the patentee's puts the pharmacist or chemist in difficulties. If the chemist had no cibazol when prescribed, should he dispense thiazamide, in which case he lays himself open to attack by the patentee. The only plan therefore is for the physician to use the chemical official name which cannot be patented.

Instance comes to ones mind of a patient, a professor of economics, having a heated argument with the writer when cardophylline that was prescribed for

his heart condition by a doctor was not available. The writer offered him aminophylline that he happened to possess as physician's sample. The professor said that the two cannot be the same as cardophylline obviously means for the heart while aminophylline must contain amino acids for nutrition. It is confessed that the official name Theophylline *cum* aethylene diamine is a bit unwieldy, but by its use the learned professor's argument that tended to raise his blood pressure (rendering null and void his treatment with vasodilator) could have been avoided.

Unfortunately the new British pharmacopoeia has not enforced discipline with regards dosage although a step has been taken in giving both the imperial and metric dosage. The tendency is for the metric system to become universal.

The new B. P. has also introduced some changes in the names like ipomea for scammony, ouabain for strophanthin; the soluble baribiturates being designated sodium barbiturates and nupercaine emerges as cinchocaine. Instead of pulverata, the word *preparata* is substituted. Preparata like digitalis, ergota, opium, nux vomica being administered as such while pulverata, forty-four in number, are in the main used for making various pharmacopoeial preparations.

One would like to rapidly survey the outstanding changes in the 1948 British Pharmacopoeia in a little more detail.

Deletions

Few will lament the passing away of hoary remedies whose title deeds to therapeutics are lost in antiquity. They include copaiba, buchu, sandal wood oil, asafoetida, drugs which were once deemed effective urinary disinfectants, asafoetida counted a 'specific in hysteria'. A few others were sacrificed with an easy conscience as they have objectionable side effects *e.g.*, methyl sulphonal, carbromal, jalap, chrysarobin (replaced by dithranol), cantharidin, sulphapyridine (the once famous M. & B. 693 that is supposed to have cured Mr. Churchill of pneumonia in Tunisia), etc. Preparations where quinine is not intended for treatment of malaria have been deleted like Easton's syrup, tr. cinchona co, ferri et quinine citras, tr. quinine ammoniata, etc.

Lancet bemoans the burial of hexamine in the words "even if the sulphonamides have ousted hexamine, it is undoubtedly a potent drug in large doses." This is a matter of opinion, for hexamine is a much misused drug for disinfecting not merely the urinary tract but to disinfect gall bladder, sinuses in cold, meningeal space etc. Even its action, alleged to be due to the release of formaldehyde in acid environment seems to be in doubt. One feels therefore that it goes without a tear.

A few set of preparations have been discarded because more active preparations are now preferred *e.g.*, dry extract of liver, powder of vitamin B, injections of iron, mercury and calomel, Easton's syrup, antidysenteric and antipenumococcal sera, etc.

Some paediatricians may bemoan the omission of confections as a class *i.e.*, confectio sulphuris and senna. And so do emplastra as a class find an exit.

Most fresh infusions barring calumba and quassia are replaced by concentrated infusions capable of storage. This is also a move in the right direction as it saves the dispenser in an institution needless waste of time.

The familiar black wash or lotio hydrargyri nigra is out and is replaced by lotio calamine, the solitary representative of the group lotions.

With liquor quinine ammoniata also exit liquor epispasticus and liquor arsenic et hydrargyri iodi, the once popular Donovan's solution.

Admissions

The outstanding group-admissions are the 'Injections, 'Tabella' and 'Cremora':—

The status assigned to *injections* (six increased to eighty-four) is presumably in tune with the times that the patient of today is more impressed with an injection than a bottle of medicine. Some of the new arrivals in the group of injections are really familiar one like morphine, adrenaline, atropine, arsphenamine, strophanthin, etc., only made immediately available in a convenient form. The modern trend to use pure chemical substances in an injection form for rapid and certain effect is reflected in the inclusion of injectio digoxin (America seems to prefer digitoxin), mepacrine, methanosulphonate, pethidine hydrochloride, ergometrine malleate etc. Hormonal preparations are put on a firm basis by the inclusion of injectio desoxycorticosterone acetate, progesterone, testesterone propionate etc. Vitamins now available in injectable form are given recognition in injectio menaphthonum, aneurine hydrochloride etc. Parenteral sulphonamide administration is also admitted by the inclusion of injectio sulphathiazole sodii, injectio sulphadiazine sodii etc.

The old pituitary extract is trifurcated into injectio posterior pituitary, oxytocin and vasopressin. A new injection not familiar to many is injectio aethanolamine oleatis (0·9 per cent, 2 to 3 c.c.) used as a sclerosing agent in the treatment of varicose veins. Out of the 15 injections of 1932 B.P. five find an exit like injectio ferri, injectio hydrargyri, injectio sodium morrhuate etc. One fails to understand why injectio sodii chloridi et acacia of the 1932 B. P. has been replaced by Ringer solution or injectio sodi chloridi composita. Notable miscellaneous injections include those of diodine and iodoxyl (for pyelography), suramin, stabophan, sodii thiosulph, sodi aurothiomalleate (or myocrisin), picrotoxin that has an established value in barbiturate poisoning, hydnocarpus oil and its ester, antimony sodi and potassi tartarate, the early antimony

preparations reasserting themselves despite urea stibamine and neostibosan. Altogether the 1948 B.P. list of injections numbering eighty and odd is very impressive. Parenteral medication as the route of choice gauged by efficiency, economy and energy seems to have gained recognition.

Tabella—Since the advent of the sulpha drugs and vitamin products in the form of tablets and the popularity of this form of medication with the public, tablets are recognised in the latest pharmacopoeia. The 1932 B.P. had just one tabella *i.e.*, glycerylis trinitratis, though the 7th addendum included erythrol tetranitrate. The sublingual administration with evidence of better absorption here than in the stomach necessitated the inclusion of tablet form of the vasodilator. The non-recognition of tablets till now was due to the fact that when made by compression the tablets are often so hard and sometimes insoluble that they escape absorption and are often detected in the faeces. The specific methods prescribed for tablet making in the B.P. 1948 *i.e.*, moist granulation or dry granulation or granulation by preliminary compression, seem to be intended to overcome the possible risk of nonabsorption.

There are 49 tabella in the new B.P. including the familiar sulpha compounds, various vitamins like ascorbic acid, nicotinic acid, acetmenaphthonum, aneurine hydrochloride etc., alkaloidal tablets like ephedrine, codeine, atropine, etc., several popular analgesics like aspirin, phenacetin, Dover's powder, etc., singly or in combination (some of the familiar proprietary ache tablets like veganin, saridon, etc., having secured recognition), hormones like thyroid, testesterone, progestin, a synthetic form of it named aethisteronum, hexoesterol, dienoestrol etc. It is interesting to note that of the sulpha compounds, sulphanilamide, sulphathiazole, sulphadiazine, sulphacetamide, sulphaguanidine and succinyl sulphathiazole alone have gained recognition. Sulphapyridine, prontosil, proseptasine etc., are passed by. If one may venture a forecast, sulphaguanidine, sulphacetamide and succinyl sulphathiazole may have a short lease of life; for the other three promise to be 'all comprehensive' between them.

The size of the tabella varies, the maximum size being half a gram. Dosage is in terms of the active principle always. The dosage of Sulphaguanindine is given as 0·5 to 2 Gm like those of sulphathiazole and sulphadiazine while the dose of succinyl sulphathiazole is given as 0·25 Gm. per pound.

Cremora—These are just elegant versions of unguenta or pasta. The designation cream or cremora sounds less of a medicament and they are also looking more elegant, like to cosmetic creams. 500 units of sodium or calcium penicillin are to be in a gram of the cremora incorporated with hard and liquid paraffin, emulsifying wax and chlorcresol for mild sterilising. The preparation cremor penicillin sterilisatus without chlorcresol but sterilised by autoclaving and with more water is intended for injection intramuscularly. There is also an unguentum penicillin. The two external medicaments of penicillin are yet to establish their utility.

Other new entrants—In the group of general anaesthetics are included aether vinilicum or divinyl ether and trichlorethylenum or trilene. The former is deemed of value in short operations particularly over the nasopharyngeal region, while the latter is finding an important place in the treatment of trigeminal neuralgia. Cyclopropane is already included in the 7th addendum.

The closely allied tetrachlorethylene has secured official recognition as a safe anthelmintic against hookworm.

Phenytoin sodium better known as dilantin sodium, a valuable anticonvulsant has become official. Amongst opium derivatives the notable change is the admission of papaverine (injection) as a valuable antispasmodic with a status equivalent to injectio etheophylline aethylenediamine and the new pethidine hydrochloride. (Pethidine is also analgesic). A significant change in the outlook is also noticed in the incorporation of codeine and even Dover's powder with aspirin as analgesics. Though so far one failed to notice in the innumerable patent analgesics like aspro, saridon, veganin, novalgin, cibalgin, sandoptol etc., any inclusion of opium derivatives, the lead by the B.P. may tend to open the flood gates.

In the cardiac group of drugs introduction of tabella digitalis pulverata and tabella digoxin are no less noteworthy than the change in the nomenclature of strophanthin to ouabain. Infusion of digitalis is no more official. One is eagerly looking forward to the inclusion of digitoxin and the products with predominant vasoconstrictor sympathomimetic action. Substances claimed to have the latter action *i.e.*, predominant peripheral vasoconstrictor action without the cardiac accelerating or cerebral action like synephrin, propadrine, methedrine etc., have not yet been recognised. Similarly on the parasympathetic side, atropine substitutes like syntopan, neurotrasentin, eumydrin etc., have not secured recognition except pethidine which has the added analgesic effect.

Thiouracil and methyl thiouracil are now included in the B.P. The list of vaccines have increased from 3 to 8 or more, including acne vaccine, cholera, pertussis, staphylococci, Flexner dysentericum, typhus and yellow fever vaccine There are several modifications in the list of vaccines, sera and toxins that it is difficult to comment. The toxin list has included those of staphylococcus, and tuberculinum. The sera list has deleted antidysenteric and antipneumococcal sera.

It is hoped in concluding that the medical profession in the use of drugs would give heed to recognised medicaments as embodied in the B.P. and would also submit itself to the medical discipline in the choice, designation and dosage of therapeutic substances.

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RURAL MEDICAL RELIEF

Recently Rural Medical Relief is receiving much attention of the provincial and central governments. There is no doubt that the medical relief available in the rural areas is scanty and primitive. On the other hand in the periodic epidemics rural areas suffer most. It is a good augury that with the advent of freedom the question of rural medical relief is being viewed with a new perspective. Nearly 90 per cent of the people in India live in the rural areas and the basic problem before the country is the provision of adequate health protection to this large section of the community.

The Bhore Committee[1] discusses this problem in detail. It bases its argument and recommendation on the conception that the state should provide a complete health service as far as possible and include within its scope the largest possible proportion of the community. It also envisages that certain primary conditions essential for healthful living must in the first place be ensured. Suitable housing, sanitary surroundings, and a safe drinking water supply are pre-requisites of a healthy life. The Committee is of opinion that "under the conditions existing in the country, medical service should be free to all without distinction and that the contribution from those who can afford to pay should be through the channel of general and local taxation."

In all the plans of rural medical relief in the provinces, it is noticeable that no stress is being given on the pre-requisites of a healthy life. By that we do not mean that medical relief should be withheld till the pre-requisites are there. We have always held that everything must proceed according to a plan and no patch work should be started as a sop to the public demand.

It is a fact which government must face boldly that there are not enough doctors in the rural areas. Qualified doctors have always settled in towns for their living. If a doctor has got to live he must earn and there is no doubt that towns are better in this respect than villages. A professional man who has passed successfully through arduous and prolonged scientific education is not generally willing to reside in a remote country area where amenities of life are few and earnings meagre. The solution will be found in improved communication and increasing use of mechanical transport by the doctor who has initiative, while the sick man will himself by the same means be able to travel to the nearest dispensary or hospital with less difficulty than is often imagined. We must say the problem has not been correctly approached by some provincial governments. Col. Amir Chand[2] in an illuminating article exposes the method of a certain provincial government regarding medical relief. The said government is considering the proposal whereby every newly passed medical student shall be required to render compulsory service in a rural area for a period of one year before he or she would be granted a degree or diploma and that during the period of such service he or she will be granted a sum of Rs. 50 per month as out of pocket expenses and the service will be considered as approved if it was certified by the Civil Surgeon of the district as such. We draw the attention of our readers to this article where Col. Amir Chand has shown that if this method is followed, it will help neither the rural population nor the doctor concerned and in his opinion such a move is dangerous and retrograde.

The efforts of another provincial government for rural medical relief are described in a communication to this Journal.[3] We have no official communication denying this press report on which the letter is based. The provincial government have decided to start a medical school to which it is proposed to admit 56 students' in the first instance. This school will have a 3 years course and a revised syllabus and students who have passed the matriculation examination will be eligible for admission to the school. It is understood that these 'doctors' will be allowed to practise in villages only and this move has been taken by the provincial government to meet the great shortage of medical practitioners in the rural areas.

One is amazed at the lack of a sympathetic attitude towards a villager. The argument seems to be that a halfbaked doctor is better than a quack. But this is a dangerous argument because it is difficult to prove who is the worst quack. We are forced to conclude that the government have never seriously considered the reasons why doctors do not go to settle in rural areas nor have they taken any steps to implement the Bhore Committee's report, even partially.

We only ask why this conscription and why this indecent haste to manufacture halfbaked doctors or quacks with official recognition? If it is a question of conscription it must also include all other professions as Col. Amir Chand forcefully argues in his article. Instead of making halfbaked doctors have the government seriously tried to attract the medical profession to the rural areas? Instances are not rare in other civilized countries where similar problems had to be faced. Did the government care to enquire how these problems were solved there? In the Highlands and Island service of the north of Scotland and in certain British colonies, the promising method has been to subsidize the practitioner or to provide him with transport or travelling allowance. Even in Soviet Russia there are special amenities like free house, a free car, longer holidays with full pay etc.[4] for practitioners in sparely populated areas.

The doctor must be given a living wage, the necessary amenities of life and facilities for education of his children before he can be attracted for a rural practice. Government should understand that a contented doctor will be more useful for the purpose for which he is being sent. The Indian Medical Association has offered its hand of co-operation to the government since August, 1947. There is no reason why the government should not accept its hand of co-operation to solve this important and difficult task.

[1] Health Survey and Development Committee, Vol. IV, p. 5, 1946.
[2] Amir Chand, *J. Indian M. A.*, **17**:358, 1948.
[3] Rao, U. B. Narayan, *J. Indian M. A.*, **17**:401, 1948.
[4] Editorial. *J. Indian M. A.*, **11**:352, 1942.

NOTES AND NEWS

THE 3RD ANNUAL CONFERENCE OF GUJARAT, CUTCH AND KATHIAWAR

Under the auspices of the Gujarat and Kathiawar Provincial Branch, I.M.A., 3rd Annual Conference of the medical men of Gujarat, Cutch and Kathiawar will be held at Surat in March, 1949. The reception committee has been formed under the able chairmanship of Dr. M. K. Dixit. Papers on important scientific subjects will be read and discussed by eminent medical men of the province. It is also decided to have an exhibition of surgical and medical appliances and pharmaceutical products. For further particulars please communicate to Dr. K. H. Haradwalla, Organising Secretary, Vanki-Bordi, Surat.

ALL-INDIA DENTAL CONFERENCE

The Fourth All-India Dental Conference has been invited to hold its session in Calcutta on February 5, 6 and 7, 1949 by the Bengal branch of the All-India Dental Association.

The honorary organising Secretary of the Reception Committee announces that the Governor-General of India, H.E. Sri C. Rajagopalachari has consented to be the patron of the conference.

STUDY OF DENTISTRY ABROAD

The following candidates have been selected on the Central Selection Board for advanced training abroad in dentistry under the Government of India scheme:

Central candidates: 1. Mr. Prem Prakash, 2. Mr. Daman Lal, 3. Capt. T. Chudgar.

Provincial candidates: 1. Dr. T. N. Chawala (U.P.), 2. Dr. Hari Dayal Gupta (U.P.), 3. Dr. A. N. Khandadia (Bombay), 4. Dr. Kashi Nath Paul (West Bengal).

States: 1. Dr. Brij Bahar Singh Marya, (Patiala), 2. Dr. Ram Pratap (Nabha), 3. Dr. Joginder Singh (Faridkot).

RESEARCH IN MENTAL DISEASES

Following the recommendation of the Bhore Committee, the Upgrading Committee appointed by the Government of India has selected the Mental Hospital, Bangalore, as a centre for research and post-graduate study in mental diseases. Dr. M. V. Govindaswami, Superintendent of Bangalore Mental Hospital, will be the Director of post-graduate study and research.

LADY TATA MEMORIAL TRUST

The Trustees of the Lady Tata Memorial Trust announces the award of the following scholarships and grants for the year 1948-49.

International Awards for research in diseases of the blood with special reference to leucaemias.

1. Dr. Jorgen Bichel, Denmark, 2. Dr. Johannes Clemmesen, Denmark. 3. Dr. C. F. M. Plum, Denmark. 4. Dr. Simon Iversen, Denmark. 5. Prof. Edoard Storti, Italy. 6. Dr. Pierre Cazal, France. 7. Dr. Guido Totterman, Finland. 8. Dr. Peter A. Gorer, England. 9. Dr. Edith Paterson, England. 10. Dr. M. C. Bessis, France. 11. Dr. A. Kelemen, Hungary. 12. Dr. & Mrs. Paterson, Christie Hospital and Holt Radium Institute, Manchester, England.

Indian Scholarships of Rs. 250 per month each for one year from 1st July 1948 for scientific investigations having a bearing on the alleviating of human suffering.

1. Mr. Suprabhat Mukherjee, (Applied Chemistry), Calcutta. 2. Mr. Yashwant Balkrishna Rangnekar, (Biochemistry), Bombay. 3. Mr. Gangagobinda Bhattacharya, (Diabetes), Calcutta. 4. Mr. K. Ramamurti (Biochemistry), Bangalore. 5. Miss V. Shanta Iyanger, Bombay. 6. Mr. B. K. Sur (Biochemistry), Bangalore.

CLINICAL TRIALS OF NEW REMEDIES UNDER THE I.R.F.A.

The Secretary, Governing Body and Scientific Advisory Board, in addressing all hospitals in India, Indian Research Fund Association, New Delhi, writes:

The Governing Body of the Indian Research Fund Association has on the advice of its Scientific Advisory Board, decided to establish under its auspices a 'Therapeutic Trials Committee' to sponsor and coordinate clinical research on new therapeutic agents. This Committee will encourage and aid impartial clinical trials of biological, chemotherapeutic and pharmaceutical agents of Indian or foreign origin, which offer promise in the prevention, treatment and diagnosis of diseases. The Medical Research Council of the United Kingdom and the Council of Pharmacy and Chemistry of the American Medical Association have set up similar bodies in their respective countries and it is considered that the time is now ripe for the initiation of such an organisation in India also. The Committee constituted by the Scientific Advisory Board of the I.R.F.A. for the purpose is as follows:—

1. Dr. M. G. Kini, late Superintendent, Stanley Hospital, Madras. 2. Dr. B. Mukerji, Director, Central Drugs Laboratory, Calcutta. 3. Lieut.-Colonel Jaswant Singh, Director, Malaria Institute of India, Delhi. 4. Dr. J. C. Patel, Honorary Assistant Physician, K. E. M. Hospital, Bombay, (Secretary).

This Committee is empowered to co-opt other members as and when required and its functions will be:—

(*i*) to frame rules and regulations for the conduct of clinical trials;

(*ii*) to obtain necessary information regarding facilities available in different institutions in India for this type of work. This information will be obtained through the office of the Secretary, Indian Research Fund Association;

(*iii*) to decide in the first instance on the suitability of any particular drug for clinical trials; and

(*iv*) to collect data regarding suitability of the place and personnel who should be invited to undertake clinical trials of a particular type of drug.

The conditions under which the Indian Research Fund Association will be prepared to undertake clinical evaluation of new remedies of Indian or foreign origin submitted by the manufacturers have been drawn up on the analogy of those adopted by the Medical Research Council of the United Kingdom and a printed copy of this is enclosed for your information. To carry out satisfactorily clinical trials of such agents the Association will naturally require the co-operation and help of all medical institutions in India which have facilities for such work and with this end in view I write to request you kindly to let me know at your earliest convenience whether your Institution would be prepared to undertake clinical trials on behalf of the Indian Research Fund Association when asked to do so. It is requested in this connection that you would be so good as to fill in the attached questionnaire giving information under the various heads required by the Committee and send it to this office as soon as possible.

Facilities available in . . . . . for the conduct of clinical trials.

1. Name of Institution:

2. Number of beds with the number of specialists and junior medical officers attached to each division.

(*a*) Medical:
(*b*) Surgical:
(*c*) Gynaecology & Obstetrics:
(*d*) Ophthalmology:
(*e*) Chest Diseases:
(*f*) Others:

3. Is there a separate Children's hospital?

4. Is there a separate Dermatological ward?

5. Number of beds that can be set apart in each ward for controlled clinical study without hampering the routine work.

6. Does the Institution maintain an Out-Patients' Department? If so, the average attendance (monthly or weekly) and the types of cases treated may be stated.

7. (*a*) Is there a clinical diagnostic laboratory attached to the different hospital divisions?

(*b*) Are there arrangements for post-mortem examination and pathological and bacteriological examinations?

(*c*) Is there a separate laboratory for haematological and biochemical work of the hospital patients?

(*d*) Indicate the special types of laboratory tests, e.g., liver function tests, kidney function tests, gastric test-meal analysis, B.M.R., etc., that are commonly undertaken in your hospital.

(*e*) Are there arrangements for pharmacological testing and determination of toxicity in laboratory animals of unknown medicinal agents?

(*f*) Is there any arrangement for graphic recording?

(*g*) Is there any arrangement for radiological examination and physio-therapeutic applications?

8. Is your Institution recognised as a Teaching Centre? If so, what is the number of members of the teaching staff in each department?

9. Is it recognised for post-graduate training? If so what courses of study are offered?

10. Is your Institution prepared to undertake clinical trials on behalf of the Indian Research Fund Association. If in the affirmative please suggest names with qualifications of officers who wish to be on the panel. It may please be stated whether they have undertaken any work of this kind before and details of such work furnished.

11. State the facilities available in your Institute for (*a*) clinical research and (*b*) basic research. Would the existing facilities, in your opinion, be adequate for conduct of clinical trials or would further help be needed? If so, a brief statement of the type of help that would be needed may please be given.

12. Is any research work being conducted at your institution with the aid of the funds of the Indian Research Fund Association or any other body or independently?

CHLOROMYCETIN IN RICKETTSIAL INFECTIONS

The efficacy of the antibiotic, chloromycetin, in scrub typhus is likely to prove a discovery of capital importance. The first results of the Anglo-American clinical trial proceeding in Malaya suggests that we at last have a potent remedy for the rickettsial diseases. The antibiotic was isolated in 1947 by Ehrlich and colleagues (*Science*, **106**:417, 1947) in Detroit from a soil actinomycete, and its active principle, obtained in crystalline form, was found to differ from any antibiotic so far described in containing both nitrogen and non-ionic chlorine. In laboratory infections chloromycetin, weight for weight, appeared more effective against *R. prowazeki* in chick embryos than any other agent tested under these experimental conditions, and large doses produced no symptoms in animals. These encouraging laboratory results demanded clinical trial in human typhus infection, and satisfactory results were claimed in a few cases of epidemic typhus in Mexico early this year. Since March, Smadel and other research-workers from the U.S. Army and the University of Maryland have been collaborating with Lewthwaite and Svoor of Kuala Lumpur in a clinical

trial in scrub typhus, and preliminary results were reported at the International Congress on Tropical Medicine at Washington, D.C., in May.

Scrub typhus, or tsutsugamushi fever, was one of the major medical problems of the Burma campaign. The disease is indigenous to a large part of tropical and subtropical Asia, but its extent was not realised until large numbers of troops were put into jungle previously unvisited by white men. It has long been recognised in Malaya, and much work has been done on it there by Lewthwaite and his colleagues at the Institute of Medical Research, Kuala Lumpur; so it is fitting that this institute was chosen as the headquarters of the trial. The vector of the disease is a mite, not unlike our own "harvester" that picnic parties encounter in the September corn stubble, but picked up in the tropics by Walking through the lalang grass. The overgrown rubber plantations are now being cleared after the Japanese occupation and the disease, always endemic, is being encountered again among the native workers. So far 25 patients have been treated with the drug, while a control group of 12 untreated cases have been observed during the same period. The treated and untreated come from the same areas and in some cases from the same plantations, so the strains of *R. tsutsugamushi* are likely to be of similar virulence. The mean ages of the two groups—an important factor in any typhus infection—were the same. The diagnosis was proved in each instance, either by recovering the rickettsia from the blood or by demonstrating satisfactory titres for agglutination against an OXK strain of *Proteus*. In the treated group nobody developed complications or died; the average duration of fever after the first dose was 31 hours, and the average total febrile period 7·5 days; one man, treated on the 3rd day of the disease, was discharged for light work on the 9th day after onset. In the untreated group of 12, 2 patients developed serious complications and 1 of these died, while the mean duration of fever was 18·1 days. The chloromycetin was given by mouth, initially in large doses; but these were gradually reduced, and the last 7 cases were given the drug for only 24 hours, receiving a total of 6 gm. with an equally satisfactory response. Half the patients were treated on estate hospitals where nursing conditions are necessarily somewhat primitive.

To those who have had experience of scrub typhus in the Burma campaign these results will be more than striking; they will alter the whole picture of a disease. From the laboratory work it is not too much to hope that this new antibiotic will prove equally effective against other rickettsial diseases. If so, the future history of the typhus group of diseases will depend on how far the demand for chloromycetin can be met.—*Lancet*, **1**:954, 1948.

METHODS OF RAT DESTRUCTION.

In the last seven months of 1945, 75 cases of plague were diagnosed in Malta, and Barnet (*J. Hyg. Camb* **46**:10, 1948) has described the methods used to eradicate the rats carrying the infection. The island has a population density three times that of England, and conditions are favourable for the multiplication of rats, particularly in the towns and urban districts. From June, 1945 to June, 1946, out of 22,902 rats examined 659 were *Rattus rattus* and the remainder *R. norvegicus* (the brown rat). Of this total 20 rats, including 15 *R. norvegicus*, were found to be infected with *Pasteurella pestis*. Systematic rat destruction began at the end of August, 1945. The standard rat poisons—zinc phosphide, red squill, arsenious oxide, and the more recent addition, 'Antu' (L-naphthylthiourea)—were used. Plain bait was laid for four or five nights, and poisoned bait on the fifth or sixth night. A fortnight after poisoning a different plain bait was laid to test for residual infestation. Where takes of this bait were observed, baiting was continued again for four or five nights, after which a new poison was added. Cleaning and proofing of buildings were also carried out as far as possible. All farms and built-up areas, including the sewers, were systematically treated. When the control measures started, nearly all the bait was taken; six to seventeen months after treatment only 11·6 per cent of 362 test baits had been touched three days after setting. The reduction of the rat population was accompanied by a decrease in the incidence of plague and of flea-borne typhus. (*Research*, **1**:334, 1948).

According to O'Connor the rodenticides in common use all have the disadvantage that they are rapidly acting and produce acute symptoms of poisoning even when eaten in sublethal doses. This produces the troublesome condition of "bait shyness" in the rat colony and makes 100 per cent eradication difficult, even when prebaiting is used. He has therefore been studying the use as a rat-poison of dicoumarol, the active principle of spoiled sweet clover, the eating of which has long been known to cause fatal haemorrhagic disease in cattle. The average fatal dose for albino rats weighing 250 g. is 28 mg. if taken over fourteen days, whereas 30 mg. given over three days is not lethal. This necessity for a cumulative effect greatly reduces the danger of accidental poisoning. Dogs weighing 8-10 kg. survive single doses of 1 g. per kg. of body-weight and daily doses of 50 mg. administered over ten to fourteen days without developing spontaneous haemorrhages.

For initial field trials dicoumarol was added to bait at the rate of 200 mg. per lb. dry weight. Prebaiting has proved to be unnecessary, for the poison is entirely acceptable to the wild rat. The most satisfactory technique so far evolved has been to ensure that the rodents have constant and free access to the poisoned bait. The amounts eaten gradually become less as the rats become weaker and die, but the baits should be left for some time to poison the migratory rats which are the source of reinfestation. O'Connor claims that complete clearance can be achieved with dicoumarol more economically than by other methods.—*Lancet*, **1**:996, 1948.

CONTRIBUTION OF RUSSIAN SCIENTISTS TO ANTIBIOTICS

Pavel Yakimov, Doctor of Chemical Sciences, head of the Penicillin and Antibiotics Laboratory, Leningrad State University writes:

The history of penicillin, it is claimed in all Anglo-Saxon textbooks and manuals, begins with that summer morning in 1928 when Alexander Fleming, British scientist, noticed and described the inhibiting influence a spore of green mold Penicillium notatum exercises on the development of the yellow staphylococci, bacteria which cause suppurative inflammations.

We pay due tribute to the researches of Fleming who observed and described this phenomenon in 1928. We, however, are in duty bound to regard with the same respect analogous investigations conducted by Russian scientists nearly sixty years before Fleming, at the dawn of development of Russian microbiology in Russia.

In 1870-1871 two Russian physicians, V. Manassein and A. Polotebnov, have established and described in detail the bacterial and curative properties of green mold. A large 72-page monograph with 22 drawings of microscopic preparations entitled: "Relation of Bacteria to the Peniccilium glaúkum, Green Mold and the Influence of Certain Means for the Development of the Latter" written by Dr. Manassein was carried in several issues of the Military Medical Journal in 1871.

In his extensive experimental study Manassein for the first time has established—this is repeatedly proved by drawings of microscope preparations—the full disappearance and absence of microbes under the green mold surface. Manassein also drew attention to the fact that the green mold is very unpretentious as regards nutritive media, can oust other types of mold and develop even in solutions of morphia and quinine which are lethal for most other bacteria, which facts are also confirmed by contemporary investigations of Fleming and other scientists.

Several issues of another Russian medical journal "Meditainsky Vestnik" in 1872 carried a large monograph by Dr. A. Polotebnox entitled "Pathological Significance of Green Mold." In the concluding part of his study D. Polotebnov cites data for a number of experiments he made, treating with green mold various types of suppurative ulcers, furuncles and even syphilis ulcers. The treatment was so effective that he demonstrated his patients to senior students at lectures as well as during visits to the wards. The discovery of the antibacterial and curative properties of green mold by Russian scientists in the '70s of last century outstripped by far the development of science and medicine of that time. At that period the foundations of scientific microbiology were still being laid and developed by Louis Pasteur. The famous dispute between Pasteur who advanced the microbe theory of fermentation and the scientist Libich who maintained that fermentation was a purely chemical process caused by the disintegration of proteins was still not settled.

In that period when science still had no clear conceptions of the significance and biological role of bacteria, the investigations of the properties of green mold conducted by Russian scientists were so much in advance of the general development of science in these fields that they could not be further developed. Even though Dr. Polotebnov has clearly demonstrated the importance of green mold as a curative means the primitive technique of pharmacology in those days made it impossible properly to develop the findings of the Russian scientists. It was precisely for these reasons that the initial works of Russian scientists, who pioneered in new branches of learning, found no further elaboration.

It should be noted that Russian scientists resumed time and again the study of green mold. For example, in 1877 Dr. Lebedinskyy in his dissertation on the etiology of the green mold for the organism noted that though gastric juices reduced substantially the antibacterial properties of green mold, at the same time the number and types of bacteria in the intestinal tract sharply diminished. In 1904 M. Tartakovsky, a veterinary doctor, published in the "Archive of Veterinary Science" a lengthy article on exudative typhus and chicken cholera in which he describes the swift perishing of the bacteria, of exudative typhus under the influence of green mold which develops on the surface of infected blood. *These facts prove the undisputed priority of Russian scientists in the discovery of the antibacterial and curative properties of green mold, subsequently discovered again in Britain in* 1928-1940. These separate facts represent only isolated instances in the history of the modern science on antibiotics, which has developed on the foundations of the doctrine (concerning antagonism and struggle among different species of unicelled organisms) evolved by Ilya Mechnikov, great Russian scientist.

This is how Louis Pasteur described in 1887 significance of the works of Ilya Mechnikov, then still a young scientist:

"While all my young collaborators are skeptical about your theory, I at once sided with you, because I myself have for a long time been amazed by the spectacle of struggle between various microscopic organisms which I have had occasion to observe. I think you have landed on the right track. . . ."

Mechnikov's subsequent discoveries relating to the struggle among micro-organisms have not only brought him immortal fame and added to the glory of Russian science but have also mapped out for many decades the course for further researches.

We now are witnessing the triumph of Mechnikov's ideas. The science on antibiosis and antibiotics which is swiftly developing on the foundations of Mechnikov's theory is yielding splendid results.

Nearly seventy years ago Mechnikov has established the highly significant fact of intra-cellular

digestion of some microbes by others. He discovered and proved that the living unicellar organisms which are always present in our blood, the leucocytes, can swiftly be mobilized by the human body and sent along the blood stream in vast masses to inflamed parts of the body affected by microbes which have penetrated there. The leucocytes envelop the invaders and then swiftly digest them. Most of the microbes who penetrate into our organism are destroyed by leucocytes. This property of the leucocytes to digest microbes Mechnikov named phagocytosis i.e., digestion of cells. And the leucocytes he renamed phagocytes.

Mechnikov's further studies established the ability of a great many diverse types of micro-organisms to produce toxic substances which act harmfully on other microbes. Mechnikov was the first after Polotebnov to prove the possibility of utilizing for curative purposes this antagonism among different bacteria, by employing those which cause no harm to the human body to combat those which carry infection. Mechnikov proved that by introducing into the intestinal tract Lactobacillus acidophilus which are harmless to man by many of the infection-carrying bacteria present in the tract were destroyed. Mechnikov's further researches dealt with a study of the causes as to why microbes were susceptible to the toxic substances immune to other such substances now called antibiotics produced by other microbes. Mechnikov's discoveries charted the path for further investigations to scientists the world over.

The cardinal task of modern antibiotic science is the comprehensive study, separation, specification and investigation of the properties and chemical composition of the various toxic substances or antibiotics produced by various micro-organisms. The main aim of modern investigation is to find such micro-organisms which like peniccilium could produce antibiotics effective against the most virulent microbes, while being at the same time harmless for the leucocytes and erythrocytes as well for the entire organism of man and animals.

Particular efforts are now being devoted to the search of antibiotics against the bacteria of tuberculosis, typhoid fever and typhus which are immune to penicillin.

The ideas and investigations of Mechnikov and his Russian collaborators—microbiologists Bezredka, Tarasevich, Zabolotny and Camaleya have been extended and developed by scientists in the Soviet peroid—N. Krasilnikov, A. Imshenetsky, Z. Yermolyeva, G. Gause, M. Brazhnikov, P. Kashkin, M. Fisher and others.

Russian biologists have always been in the front ranks of world biological science. All modern theories on antibiotics are founded on their works. Today Soviet scientists are successfully developing the ideas first propounded nearly eighty years ago and are perfecting the technology for obtaining penicillin and other antibiotics.—U.S.S.R. News Letter.

CORRESPONDENCE

WEST BENGAL GOVERNMENT APPOINTMENTS AND L.M.F. DOCTORS

Sir,—I am inviting your attention to an advertisement dated 15-6-48 inserted in the *Amrita Bazar Patrika*, Calcutta, by the Secretary, Public Service Commission, West Bengal. In it 13 medical officers are wanted for thana health centres in West Bengal. Qualifications required are M.B., L.M.S. (Cal.) or L.M.S. (Nat.), or M.M.F., but the Government is not willing to take L.M.F. doctors to fill up the posts though it is ready to take doctors up to M.M.F. standard. British Government created the difference but the National Government is maintaining the difference. Lt. Col. Amirchand in his presidential address in A.I.M. Conference at Bombay has rightly commented *re.* the union of I.M.A. and A.I.M.L.A., "Vested interests no doubt have been in existence which have up to this time been doing their worst to prevent the union of the two Associations (I.M.A. and A.I.M.L.A.) so that they, by keeping the profession divided, may have no difficulty in curbing its activities and in controlling the medical services in their own way." Though the I.M.A. and A.I.M.L.A. are trying to remove the difference between an M.B. and L.M.F., the diehards are still playing the game to maintain the difference.

May I, therefore, request the West Bengal Government to consider it favourably and to fill up the posts with L.M.F. doctors also. I am etc.

SUSHIL KUMAR SAMONTA,
Member of I.M.A., Chapra Branch, Bihar.

Chapra, 24-6-48.

SPRUE AND SPRUE SYNDROME

Sir,—With reference to certain queries raised by Lt. Col. Amirchand *vide* Vol. XVII No. 10 p. 344 of your journal the following are my answers:—

Sprue and sprue syndrome ultimately mean the same thing. I have used the expression "sprue syndrome" in order to emphasise the symptom complex or aggregate symptoms of a disease called sprue. I maintain that there are phases or stages of disease, symptoms of which can be grouped. Thus the first phase or the stage of (onset) reveals itself in diarrhoea, anorexia and vomiting, weakness and loss of weight but no glossitis, distention or flatulance. Second stage is the stage of 'remission,' predominant symptoms of which are glossitis (sore tongue and cheilosis), dyspepsia (distension and flatulence), polyphagia, scaling of skin, but abatement of diarrhoea and gain in weight. Third stage is the stage of 'relapse' where diarrhoea becomes accentuated, anorexia becomes pronounced, emaciation and anaemia are added to a greater degree. Fourth stage is the stage of 'classical syndrome', so well known to all. The first and second

stages constitute 'acute sprue mild.' Third stage is that stage where dehydration and death may supervene and then constitutes (acute sprue severe). Fourth stage is the classical sprue. It is not necessary that the fourth stage must come in the wake of third stage straight away. From the third stage, there may be many cycles of relapse and remission covering a period of years with various combinations of symptoms peculiar to the two phases until at last the patient drags on into the classical sprue or final stage.

Thus I maintain that (*i*) it is not necessary for sprue to present itself in the form of the book picture, before it should be entitled to recognition, (*ii*) just as it is not necessary that the last stage of tuberculosis must close the scene, so is it not necessary in sprue, that classical sprue must close the scene. Fatalities (my figures 10 per cent) do occur in earlier phases when in the third stage dehydration creeps in and death quickly supervenes. Salts, sulphaguanidine, blood transfusion and liver therapy then, carry the patient from jaws of death through remission into recovery. All the four stages in aggregate constitute what I call "sprue syndrome," whereas the last stage is the one commonly called the "classical sprue". But it would be correct to call even the earlier stages by the name of sprue.

If Lt. Col. Amirchand had read my earlier paper published in the *Indian Medical Gazette,* Vol. LXXXI No. I he would not have said that I have adduced no proof of accuracy of diagnosis of sprue in the case of at least second post mortem whose findings were allied to those of the case referred to by Lt. Col. Amirchand. Even this first case was on retrospect a clinical case of sprue. What does it matter if the pathologist did not label it sprue? All that he says is that it is something he can't come to any conclusion, can't understand it and therefore calls it "unknown aetiology." Don't we recognise and diagnose diseases after death and post mortem? It turns out to be that rare problem which falls to the lot of an observing and enquiring clinician to solve. If Lt. Col. Amirchand had perused my original paper presented before the gathering of over one hundred medical pandits of the Indian Army, his confusion would not have become worse confounded.

I am however very glad that Lt. Col. Amirchand has raised these queries, because the treatment of this syndrome in its earlier stages promises better prospects of cure and we must become alive to what Rogers and Megaw said in 1942: "Any unexplained diarrhoea of more than 10 days duration should be treated as sprue, provided amoebic disease is excluded." I am etc.

P. V. KARAMCHANDANI

Bellary, 10-8-48.

REORGANISATION OF MEDICAL EDUCATION

Sir,—The medical profession is suffering from too many complexes, as graduates, licentiates and other practitioners of indigenous medicine existing in it. The slogan that the British have been the cause for the watertight compartments in the noble profession to serve their own ends can no longer hold good after India has won her full freedom and the representative Government is ruling it. The profession cannot ethically be improved and standard of its efficiency raised, unless the Government desired to establish one standard of medical education and examination of the University type with one kind of basic qualification, as is the case in America where M.D. is the only one basic qualification for the whole country. This sort of re-orientation and unification will certainly enhance the status of the profession in India in the eyes of the medical world at large and stimulate further the genius of the medical people for research. It should be the aim and object of the Government to see that there shall be only one administrative head for the province with only one Medical Council to control the profession ethically. Homeopathy and indigenous systems of medicine should be given the place of post-graduate study. It is not wisdom, if the Government should entertain the view that there should be cheaper medical men available for service, because the Government cannot provide funds fully for the basic collegiate course. It is evidently a lame excuse. The National Government should no longer continue the old policy of 'Divide and Rule' of the profession in India. They should make a public debt, if necessary and honestly spend it for the Health Schemes or stop further extension of 'prohibition' to the remaining parts of the province. I assert that it will be the right step in the right direction to close down the institutions of indigenous systems of medicine and attach the same subjects to the existing medical colleges as part and parcel of its curriculum, or make it a post-graduate course attached to the medical colleges. To provide the medical personnel as per recommendations of the Bhore Committee, the Government should open adequate number of medical colleges in the province. It is earnestly hoped by one and all that the Government will not be so blind as to revive the long forgotten and much hated L.M.P. Course. I am etc.

G. V. HANUMANTHARAO,
Vice-President, Andhra Provincial Branch, I.M.A.

Guntur, 12-8-1948.

CURRENT MEDICAL LITERATURE

Rarer Manifestations of Herpes Zoster

Parkinson (*Brit. M.J.*, **1**:8, 1948) writes that in causing infection of the human body the herpes zoster virus shows a predilection for nervous tissue and the skin. In the classical form the brunt of the infection is borne by the sensory ganglia, the resulting symptoms being pain and a cutaneous eruption in the peripheral distribution of the fibres proceeding from the affected ganglia. Study of the rarer manifestations of the disease shows that the infection often spreads beyond these confines. In some cases in which motor symptoms occur there is clinical and pathological evidence that the anterior horn cells of the spinal cord are affected in a manner similar to that in poliomyelitis. In others the infection produces an exanthem clinically identical with that of varicella.

From the available evidence it seems no more reasonable to deduce that varicella and zoster are caused by the same virus than it would be make a similar deduction regarding zoster and poliomyelitis. It seems much more probable that the virus is capable of producing a range of clinical manifestations varying from simple motor lesions on the one hand to generalized skin lesions on the other, and that the classical form of the disease lies midway between these extremes. This clinical range might be represented as follows: poliomyelitis-like illness-zoster sine herpete-herpes zoster with paralysis, classical herpes zoster, herpes zoster with generalized eruption—varicelliform zoster (sine herpete). This suggestion is of course speculative, and it takes no account of the encephalitic symptoms which are said to occur. Nevertheless, clinically proved examples of each group are to be found in the literature, with the exception of the hypothetical poliomyelitis-like illness, and it is unlikely that evidence of this will be found in the absence of specific complement fixation tests on such cases.

Cardiac Catheterization

McMichael (*Brit. M.J.*, **1**:356, 1948) at a joint meeting of the Manchester Medical and Pathological Societies on 14-1-48 in an address on cardiac catheterization, said that catheterization of the heart was introduced by Forssman in 1929 and subsequently used extensively in Portugal, France, and Latin America for injecting radio-opaque substances so as to define vessels at the root of the lung. Cournand in 1941 was the first to report its use for the measurement of pressure in the chambers of the heart, and by the application of the Fick principle he also measured the cardias output. The method had been applied in 800 cases at the London Postgraduate Medical School without untoward incident, and its use was now spreading widely in research centres in both America and Europe. Blood never clotted on the surface of the catheter; but small pin-head thrombi occasionally formed at the tip, and some of them must have escaped into the lungs, where there was good reason to believe they were harmless. In the right ventricle the tip of the catheter might excite extrasystoles, and runs of extrasystoles might harm patients whose cardiac condition was already precarious. One death had been reported in Holland in a patient with gross disease of the coronary artery following right ventricular catheterization. This was the first known fatality in an estimated 3,000 cardiac catheterizations. With the catheter in the right auricle there were no significant risks if proper precautions were taken. The standard error of right auricular samples used for the determination of cardiac output was plus or minus 4 per cent.

Patients with cariac venus congestion and oedema fall into two groups. In the ordinary forms of heart failure resulting from hypertensive, valvular and ischaemic heart disease the cardiac output was reduced to about half the normal level. In another group in which the congestive phenomena resulted from (1) anaemia, (2) emphysema, (3) conditions in which there was an increased mechanical burden on the circulation (*e.g.*, arteriovenous aneurysm, generalized osteitis deformans), the cardiac output was raised above the normal. These high-output types of cardiac failure were recognizable not only aetiologically but also clinically: warm hands and full peripheral pulses contrasted with the cold extremities and feeble pulsation often present in the low-output group.

The immediate action of intravenous digoxin on the normal heart was to lower the output and the venous pressure. A similar reaction was the rule in high-output heart failure in which digitalis was unlikely to be of benefit. In low-output failure, however, digoxin raised the output of the heart. Venesection reproduced the action of digoxin on cardiac output. It was probable that digoxin had a primary venous pressure-reducing effect which relieved the overstrained failing heart. Digitalis acted quite as well whether auricular fibrillation was present or not. Theophylline had a similar action on the venous pressure but was also a direct cardiac stimulant. Theophylline-ethylene-diamine was of particular value in hypertensive cardiac failure, but its effect was less dramatic in mitral stenosis.

In congenital heart disease the simpler defects could often be clearly diagnosed by cardiac catheterization. An interauricular septal defect was recognized by the admixture of "arterialized" blood with venous blood in the right auricle. The cyanotic forms demanded great skill in analysis with fluoroscopic control and pressure measurements at every point. With right to left shunt the method had certain risks as tiny emboli might be serious. The selection of cases for Blalock's opeation was usually made on clinical grounds. Bing's test of falling oxygen-uptake per litre of ventilation on exercise was a valuable index of pulmonary stenosis.

Cardiac catheterization, Prof. McMichael concludes, has come to stay. Further research possibilities were indicated by Bing's recent success in sampling blood from the coronary sinus. When such sampling was combined with the nitrous-oxide method of Kety and Schmidt for measuring organ blood flow we should be able to measure the volume flow in the coronary arteries. The catheter had also been used to reach the hepatic and renal veins. New avenues of research were clearly being opened.

Snoring

Robin (*Proc. Roy Soc. Med.*, **41**:151, 1948, Ref. *Practitioner*, **160**:496, 1948) writes that snoring "is a symptom

of unbalanced breathing, caused by a combination of several physical conditions . . . . . ." Organic causes of snoring are (1) nasal obstruction, and (2) pathological changes in the pharynx. Snoring may also be due to functional dysfunctions of the central reflex governing the tone of the glosso-pharyngeal musculature. The basic cause of snoring is, of course, mouth-breathing. There are three main groups of snorers—the child, the adult and the elderly person. In the majority of children cure can be obtained by removal of adenoids and tonsils; the failures include persistent mouth-breathers and children with infective or allergic rhinosinusitis. When snoring starts in an adult it is usually due to some organic cause. The third group, elderly men and women, is the largest and the fundamental causal factor seems to be lack of tone. Treatment is classified under three headings:—(1) Irrational methods, chief among which is amputation of the uvula. This rarely gives relief, but may modify the degree and pitch of the snore. (2) Rational methods: (*a*) The removal of prevention of nasal obstruction so as to obviate mouth-breathing. In some cases the application of decongestive nasal drops before retiring produces a peaceful night; in others nasal operation may be necessary; in some benadryl therapy is beneficial. (*b*) Change of position of the head to prevent the tongue from falling back. In many persons snoring occurs only when they lie on their backs, and this can be prevented by sewing a cotton reel into the back of the pyjamas or nightdress. (*c*) Alteration of the position tongue, soft palate and jaws, by breathing, swallowing and phonetic exercises, by the wearing of orthodontic splints. (*d*) Keeping the mouth closed during sleep, by wearing an "Andresen" splint, or by placing a strip of adhesive plaster across the corner of the mouth. (3) Altering the texture of the soft palate and faucial pillars, by injection of a sclerosing solution into the pillars. This method, advocated by Jerome Strauss, has so far failed to produce a high percentage of cures. In conclusion, the author states that many a potential snorer may have been prevented by the removal of tonsils and adenoids.

Allergy in Relation to Gastrointestinal Diseases

Andresen (*Medical Times*, **76**:147-42, 1948) writes that patients who suffer from gastrointestinal symptoms and get no relief from their doctor or gastroenterologist eventually turn to cultists for relief. Failing that, they become neurotic or even psychotic as a result of their inability to obtain relief. Many of these patients may eventually do well if the last physician they go to, thinks of the well known fact that allergy plays an important role, either by itself or in conjunction with organic lesions in the causation of several gastrointestinal symptoms. While allergic manifestations such as hay fever, asthma, urticaria, eczema and even migraine are being regularly recognized, the manifestations of allergy in the gastrointestinal tract are pretty generally overlooked, although they are probably most common.

Symptoms and signs may occur in any part, or in the entire length of the alimentary tract. In the mouth, may appear canker sores, stomatitis and edema, causing pain, burning, coated and swollen tongue, difficulty in chewing and swallowing. The esophagus may show the same signs and cause cardiospasm or permanent obstruction. In the stomach and duodenum, the symptoms may be those of severe gastritis or of ulcer syndrome. Small intestine allergy may manifest itself by abdominal cramps and diarrhoea. Regional ileitis probably always starts as an allergic manifestation.

The gallbladder, appendix and colon, when affected by allergy, simulate acute or chronic diseases of the organ. In the anorectal junction, pruritis is the symptom most often complained of. The gastrointestinal tract, when affected as a whole, presents the picture of acute gastroenteritis, with nausea, vomiting, cramps and diarrhoea which will last as long as the offending allergen is being ingested.

The Spleen in Congestive Heart Failure

Fowler (*Ann. Int. Med.*, **27**:733, 1947) writes that "the spleen, on the average, is increased above the normal size in uncomplicated heart failure." This conclusion is based upon an investigation of necropsy material at the Peter Bent Brigham Hospital: 50 surgical cases used as controls, 50 cases of valvular rheumatic heart disease with congestive heart failure, 50 cases of hypertensive or arteriosclerotic heart disease, and 46 cases of subacute bacterial endocarditis. The average weight of the spleen in the different groups was as follows: surgical control group, 135 gm.; rheumatic valvular heart disease, 220 gm; hypertensive and arteriosclerotic heart disease, 198 gm; subacute bacterial endocarditis, 371 gm. Taking as his criteria that any spleen over 200 gm. is enlarged, and any over 300 gm. is clinically palpable, Fowler found that among 97 cases of uncomplicated congestive heart failure the spleen was theoretically palpable, *i.e.*, over 300 gm. in weight, in 13·4 per cent., although in only one instance had the spleen been palpated during life. This splenomegaly of congestive heart failure did not appear to be appreciably influenced by the duration of the failure or by the presence of infarcts. Another interesting finding was that in this series the spleen, on the average, showed greater enlargement than the average liver in congestive heart failure.

Procaine Penicillin G

Hervell and others (*Proc. Staff Meet. Mayo. Clin.*, **22**:561; 1947) in reporting on the results of preliminary clinical trials with procaine penicillin G (duracillin: Eli Lilly & Co.) observe; Procaine penicillin G, a crystalline non-pyrogenic substance prepared by combining one molecule of procaine base (molecular wright 236) with one molecule of penicillin (molecular weight 334), resulting in a compound containing 41·5 per cent. procaine base, is stated to have a potency of 940 units per mgm., 90 per cent. of which is attributable to penicillin G, and a solubility in water at 28°C. of slightly less than 0·7 per cent. Ten patients, some ambulatory, and some non-ambulatory were given a single intramuscular injection of 1 c.c. of an oil suspension of procaine penicillin G (300,000 units of penicillin), and the concentration in the blood was determined every three hours for twenty-four hours, starting three hours after injection. Except in one case adequate concentrations of penicillin were present in the blood twenty-four hours after injection, and in some cases for longer periods. Apart from slight pain at the time of injection there was no incidence of local irritation, soreness or pain after injection, thus suggesting that the procaine exerts a twofold action:

(1) prolongation of the action of penicillin, and (2) an anaesthetic action. The conditions treated included septic sore throat, pneumonia, lymphangitis and carbuncle. No toxic reactions were noted.

A Method for Prolonging the Action of Penicillin

Carlinfanti and Morra (*Schweiz. med. Wechnschr.*, **77**:1236, 1947, Ref. *Practitioner* **160**:75, 1948) describe a simple method for prolonging the action of penicillin and maintaining a satisfactory concentration in the blood, which is stated to produce results equal to those obtained by injections of oily solutions. The penicillin is injected by subcutaneous route into the thigh or arm after the circulation of the injection area has been retarded by the application of a rubber tourniquet, using a pressure slightly less than the minimal arterial pressure. The tourniquet must not be left in place for more than one to five hours, according to the amount of penicillin injected, *i.e.*, 10,000 to 100,000 units. Using this method the number of injections can be reduced to three of 75,000 units in twenty-four hours, or five of 100,000 units in forty-eight hours, or the quantity of penicillin injected may be reduced to 80,000 units, giving eight injections of 10,000 units in twenty-four hours. It is probable that with doses of 600,000 to 800,000 units that a single injection might suffice to maintain a satisfactory penicillin concentration in the blood for twenty-four hours. In illustrative graphs it has been shown that after injection of 16,000 units the blood concentration level was maintained for four hours, the tourniquet being removed 1¼ hours after injection; after injection of 75,000 units it was maintained for 8½ hours, the tourniquet being removed after 3¾ hours, and after injection of 100,000, the level was maintained for 8½ hours, these levels being in comparison with 2½, 4½ and 6 hours blood level concentration when no tourniquet was used. The pressure exerted by the tourniquet must be regulated by the absence of painful sensations in the limb. It is stated that with the use of this method the number of injections can be reduced and at the same time a considerable economy in penicillin usage can be effected.

Allergic Rhinitis

Criep (*J.A.M.A.*, **136**:601, 1948) writes that although allergic rhinorrhoea is affected by endocrine factors, such as pregnancy and menstruation, and by climatic conditions, irritating fumes and chemicals, emotional factors, nasal obstruction and infection, the underlying causative factor is exposure to a substance to which the patient is sensitive. Sensitization tests—cutaneous, ophthalmic and nasal—sniff tests, and trial or elimination diets to determine if the causative factor be a food idiosyncrasy, should be carried out. The ophthalmic test consists in instillation of a drop of the suspected material in the conjunctival sac: a positive reaction is manifested by local itching, congestion and lachrymation). On the basis of the diagnosis, treatment is instituted, in the form of specific allergic therapy (avoidance and hyposensitization), medicinal measures, attention to nasal infection, and psychotherapy. The patient is instructed to occupy dust-free rooms and to use allergen-proof pillows; a diet is given in which foods to which the patient is sensitive are eliminated; hyposensitization is carried out with increasing doses of autogenous extract of house dust or other substance to which the patient is hypersensitive; irritating fumes and noxious occupational factors are avoided. Medicinal treatment is directed towards palliation, and includes the oral administration of ephedrine, 0·375 grain (24·4 mgm.), and phenobarbitone, 0·167 grain (10·8 mgm.), four-hourly when necessary. The antihistamine drugs are also useful—neoantergan, 50 mgm. four-hourly; benadryl, 25 to 50 mgm. four-hourly, or pyribenzamine, 25 to 50 mgm. four-hourly—but if side-effects such as drowsiness, palpitation, nausea and vomiting occur the drugs must be stopped. Local vosoconstrictors should be used but sparingly, as their continued use causes congestion and intensification of local symptoms. If nasal drops are prescribed the Proetz position should be employed. It is stated that rhinological treatment should always at first be conservative before institution of any surgical intervention. As emotional factors play a part in the etiology, psychotherapy may be of value.

A New Substance for Asthma

Adrenaline is still the most reliable agent for the relief of bronchial asthma. In recent years it has been given not only by subcutaneous injection but as a fine spray pumped into the back of the throat and inhaled. For this purpose a 1 per cent. solution is used. When adenaline fails to give relief in more severe asthmatic attacks—for example, bronchitis—theophyline may be injected intravenously, dissolved in a suitable solvent such as ethylene diamine.

A further addition to anti-asthmatic substances is a derivative of adrenaline, the properties of which Konzett (*Arch. Exp. Path. Pharmak.*, **197**:27 & 41, 1940) described in 1940. Adrenaline has an amine group at the end of its side chain in which one of the hydrogen atoms is substituted by—CH. Konzett found that replacement of this methyl group by an isopropyl group resulted in a substance which was 10 times as powerful as adrenaline in relaxing bronchial spasm produced in the anaesthetized dog. He examined other related substances: N-ethyl adrenaline was 3 times as potent as adrenaline: N-propyl and N-butyl adrenaline were about equal in potency to adrenaline; and, finally, N-isobutyladrenaline was about 10 times weaker. The substance neosynephrine or metasympatol, which differs from adrenaline in having only one—OH group in the benzene ring, was also found to develop great power to relax the constricted bronchioles when an isopropyl group replaced the methyl group in the side chain.

Isopropyl adrenaline (now manufactured in the U.S.A. as "isuprel") has an action on the heart similar to that of adrenaline, but, unlike adrenaline, it causes a fall of blood pressure. This effect is not likely to be appreciable when isopropyl adrenaline is used therapeutically, since the amount required is so small. The properties described by Konzett have been confirmed recently by Lands, Nash, and their colleagues (*J. Pharmacol.*, **90**:110, 1947). It is to be hoped that isopropyl adrenaline will be made available in this country. —*Brit. M.J.*, **1**:261, 1948.